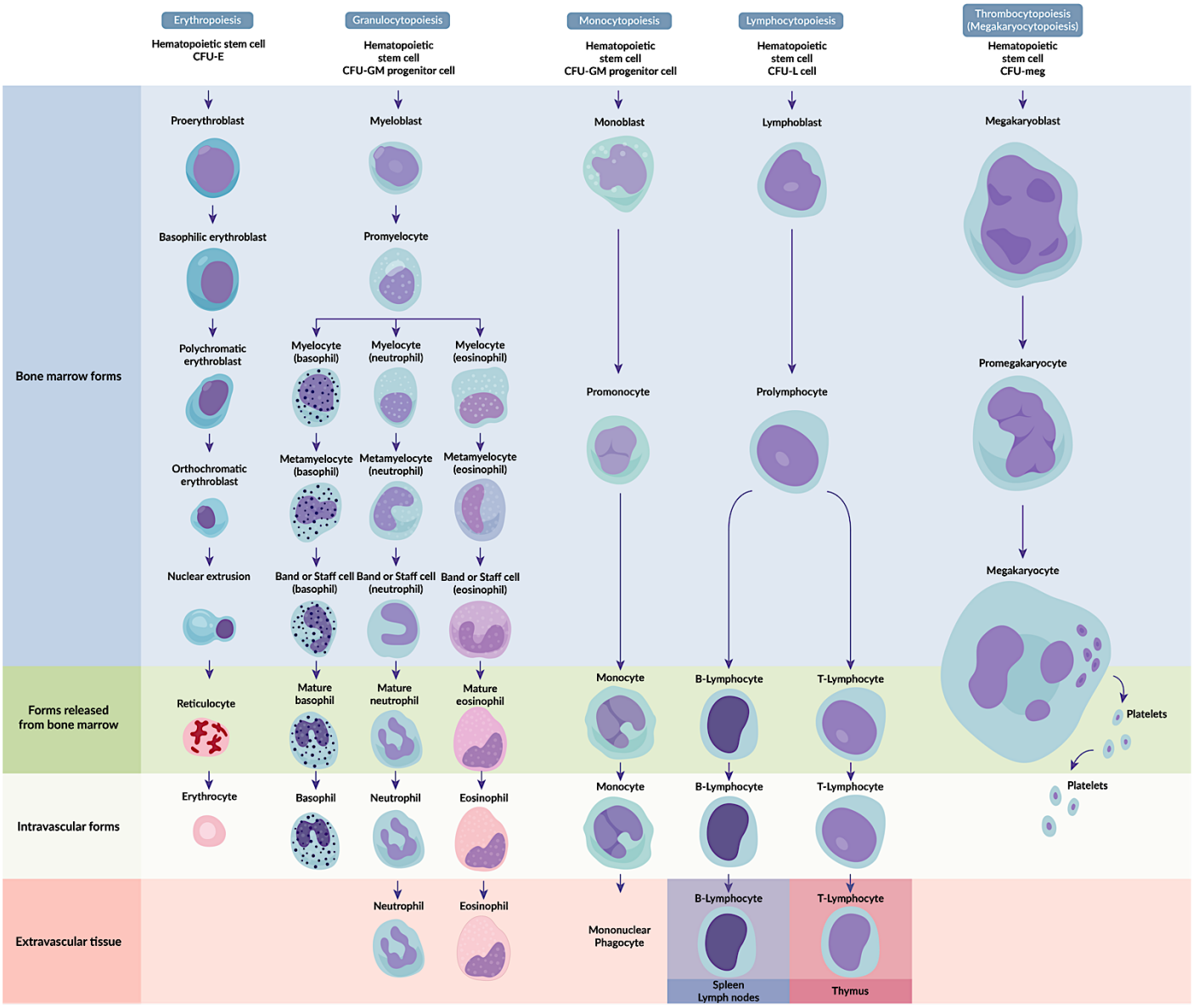
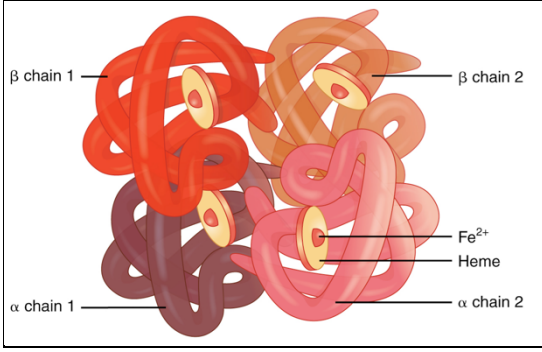
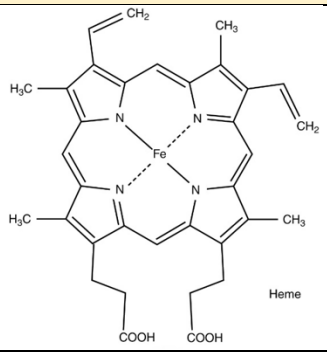
BLOOD PHYSIOLOGY

HEMATOPOIESIS



HEMOGLOBIN





Hemoglobin Structure

ANEMIA

DEFINITION	**IN MEN**	➡ *Hb <14 g/dL (normal 13.5–18 g/dL)* ***(higher Hb due to the erythropoietic effects of androgens)***	
	IN WOMEN	➡ *Hb <12 g/dL (normal 12–15 g/dL)* ***(lower Hb due to menstrual loss)***	
	VARIATION	1. *Athleticism* 2. *Ethnicity* 3. *Residence altitude*	
PRESENTATION	**ASYMPTOMATIC**	➡ *Even with marked anemia due to chronicity*	
	SYMPTOMATIC	**IRON DEFICIENCY**	1. *Fatigue/Lethargy* 2. *Dyspnea* 3. *Dizziness* 4. *↓ Exercise tolerance* 5. *Ice-eating (pagophagia)*
		IRON DEFICIENCY – RELATED THYROID DISEASE	1. *Constipation* 2. *Cold intolerance*
		B_{12} DEFICIENCY	➡ *Distal paresthesias*
		HEREDITARY SPHEROCYTOSIS	➡ *Left upper quadrant (LUQ) abdominal pain due to splenomegaly*
		CHRONIC HEMOLYSIS	➡ *Right upper quadrant (RUQ) pain or intolerance to fatty foods due to cholelithiasis*

5 MECHANISMS OF ANEMIA

MECHANISM		RETIC %	MORPHOLOGY	CAUSES	DISORDERS
PRODUCTION DEFECT		↓	*Normal*	*↓ EPO* *Bone marrow failure*	*Anemia of chronic disease* 1. *Chronic rheumatic* 2. *Infectious disease* 3. *Neoplastic diseases* 4. *CKD*
MATURATION DEFECT	**CYTOPLASMIC**	↓	*Hypochromic microcytic*	*Impaired Hb synthesis* *Globin synthesis deficiency*	*Iron deficiency* *Sideroblastic anemia* *Protoporphyrin deficiency* *Myelodysplastic syndrome (MDS)* *Drugs/Toxins* *Thalassemias*
	NUCLEAR	↓	*Megaloblastic*	*DNA synthesis defect*	*B_{12}/Folate deficiency*
SURVIVAL DEFECT	**INTRINSIC (INHERITED)**	↑	*Specific changes–* *Spherocytes* *Sickle cells* *Bite cells*	*Membrane cytoskeleton protein* *Metabolic enzymes* *Hemoglobinopathies*	*G6PD deficiency* *Pyruvate kinase deficiency* *Sickle cell disease* *Hereditary spherocytosis* *Hereditary Elliptocytosis* *Paroxysmal nocturnal hemoglobinuria*
	EXTRINSIC (ACQUIRED)	↑	*Specific changes–* *Spherocytes* *Schistocytes*	*Antibody or Complement-mediated* *Microangiopathy* *Mechanical heart valve*	*Autoimmune hemolysis* *Malaria* *TTP/ HUS/DIC* *HELLP*
SEQUESTRATION		↑	*Normal*	*Hypersplenism*	*Portal hypertension* *Sickle cell (SC not SS)*
BLOOD LOSS		↑/*Nl*	*Normal or Hypochromic*	*Acute or Chronic bleeding*	*PUD* *GI bleeding* *Menorrhagia* *Trauma*

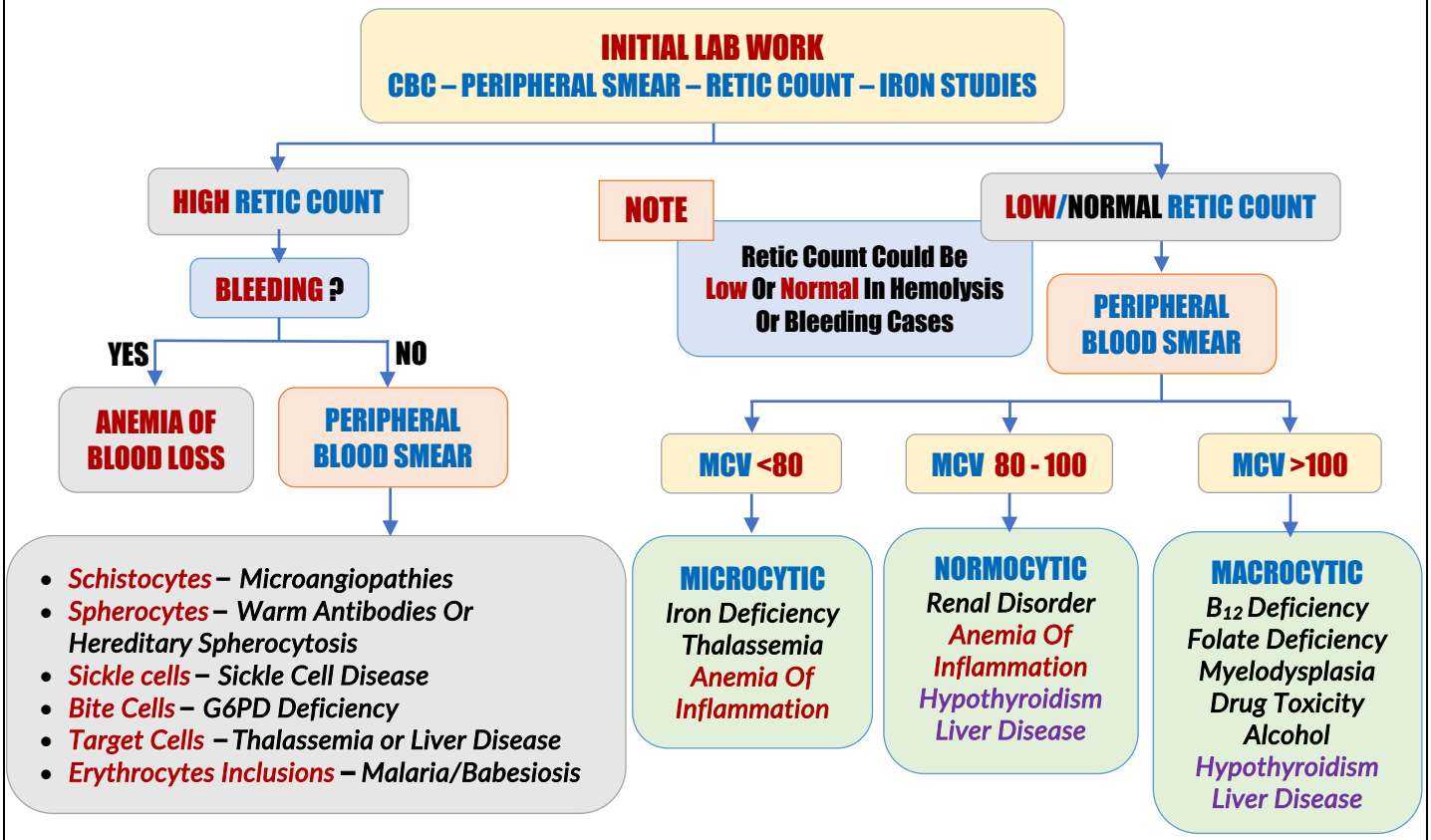
↑ if adequate iron stores
Not elevated if depleted iron stores as chronic blood loss

ANEMIA WORK UP

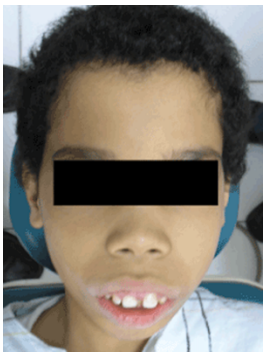
Anemia should never be taken as the final diagnosis & the underlying cause must be identified that will allow focused therapy (beyond blood transfusion) to current anemia (as iron supplement in iron deficiency anemia)

BASED ON 2 SETS OF TESTS

MORPHOLOGIC TESTS	KINETIC TEST	
1. *RBC count/Hb & Hct concentrations* 2. *Peripheral blood smear (PBS) (micro/macro/normocytic)* 3. *RBC indices –* • *Mean corpuscular volume (MCV)* • *Mean corpuscular hemoglobin (MCH)* • *Mean corpuscular hemoglobin concentration (MCHC)* • *Red cell distribution width (RDW)*	➡ *Assess appropriate reticulocytes response = intact structural & functional bone marrow response to EPO* 1. *Reticulocyte production index (RPI)* 2. *Reticulocyte count %* 3. *Absolute reticulocyte count*	
	LOW RPI & RETIC COUNT (< 2%)	1. *Production defect –* • *Myelodysplasia syndrome* 2. *Maturation defects –* • *Vitamin B_{12} or folate deficiency* • *Iron deficiency*
	HIGH RETIC COUNT NORMAL BM RESPONSE	1. *Shortened RBC survival* 2. *Splenic sequestration* 3. *Blood loss*
	HIGH RETIC COUNT + ANEMIA	➡ *Assess bone marrow with RPI → if low = combined causes with additional production or maturation defects*



BONE MARROW BIOPSY/ASPIRATE INDICATIONS	1. *If anemia cause is unclear* 2. *If suspected hematologic malignancy/stem cell disorders (lymphoma/leukomia/aplastic anemia/MDS)*

<table>
<tr><th colspan="3">β-THALASSEMIA</th></tr>
<tr><th>β-THALASSEMIA MINOR (TRAIT)
(HETEROZYGOTES = Defect In 1 Or 2 β-Globin Alleles)</th><th>β-THALASSEMIA MAJOR
(HOMOZYGOUS)
(COOLEY ANEMIA)</th><th>β-THALASSEMIA INTERMEDIA
(HOMOZYGOUS)</th></tr>
<tr><td colspan="3">PATHOLOGY
Mutation in β-globin locus of chromosome 11 → decreased β chain production & increase compensatory δ and γ chain production → increases in ineffective HbA_2 ($\alpha_2\delta_2$) & HbF ($\alpha_2\gamma_2$)</td></tr>
<tr><td>Mild reduction in β-globin production
(β^+-thalassemia)
1. Mild or no anemia (Hb 10–12 g/dL)
2. Disproportionate high microcytes number (MCV 60–70 fL)
 
Chipmunk Facies
Source: Mohamad Kharsa</td><td>Complete absence of β-chain synthesis
(β^0-thalassemia)
with secondary
high insoluble α-globin precipitates into homotetramers (inclusion body) → toxic to erythrocytes → RBCs die within bone marrow & RBCs carry inclusion bodies → removed by spleen → chronic hemolytic anemia & jaundice → elevated EPO (due to severe anemia in 1st year of life) → erythroid hyperplasia → extramedullary hematopoiesis in the liver and spleen & expanded bone marrow production in the cranial bones → facial changes in children = CHIPMUNK FACIES</td><td>In some homozygous patient → there are modulating factors –
1. Minor qualitative β-globin defects
2. Coinheritance of α-thalassemia → lead to –
• ↓ formation of toxic RBC inclusion → less precipitation of insoluble homotetramers → less hemolysis
• ↑ HbF production
• Hb level of 7 g/dL (but not transfusion dependent)</td></tr>
<tr><td colspan="3">PRESENTATION</td></tr>
<tr><td>Asymptomatic</td><td>Chronic hemolytic anemia & jaundice
Chipmunk facies</td><td>➡ Variable range –
• Asymptomatic
• Iron overload manifestation (due to ineffective erythropoiesis) –
1. Extramedullary erythropoiesis
2. Splenomegaly
3. Osteoporosis & bone pain
4. Hypogonadism</td></tr>
<tr><td colspan="3">DIAGNOSIS</td></tr>
<tr><td colspan="3">HEMOGLOBIN ELECTROPHORESIS</td></tr>
<tr><td>Abnormal Hb electrophoresis with 2–3 x ↑ HbA_2 ($\alpha_2\delta_2$) due to δ globin substitution for β globin + Slight ↑ HbF ($\alpha_2\gamma_2$) based on the specific mutation</td><td>High HbF & HbA_2
No HbA (in severe cases)</td><td>Range of HbF & HbA_2</td></tr>
<tr><td colspan="3">MOLECULAR GENETIC TESTING (CONFIRMATION)</td></tr>
<tr><td colspan="3">TREATMENT</td></tr>
<tr><td>Genetic counseling & folate supplementation (if anemic) + Avoid supplemental iron (as α-thalassemia)</td><td colspan="2">• Balancing periodic blood transfusion to ↓ extramedullary hematopoiesis with caution of iron overload
• Splenectomy (if marked ↑↑↑ transfusion/severe anemia/hypersplenism)
• Luspatercept (avoid if patient had splenectomy due to ↑ thromboembolism) –
MECHANISM ➡ Recombinant fusion protein → inhibits TGF-β superfamily → ↑ differentiation & proliferation of erythroid precursors → improves ineffective erythropoiesis
INDICATION ➡ Treatment of for β-thalassemia-dependent RBCs transfusions</td></tr>
</table>

LEAD INTOXICATION

CAUSES

1. *Occupational lead exposure (the most common cause)*
2. *Contaminated supplements or water supply*
3. *Home exposure to lead paint*

PRESENTATION

LOWER LEAD LEVEL

- *Arthralgia*
- *Myalgia*
- *Headache*
- *Abdominal pain*
- *Neurocognitive changes*

HIGHER LEAD LEVEL

- *Anemia*
- *Chronic tubulointerstitial nephritis*
- *Peripheral neuropathy*
- *Prominent neuropsychiatric changes*

DIAGNOSIS

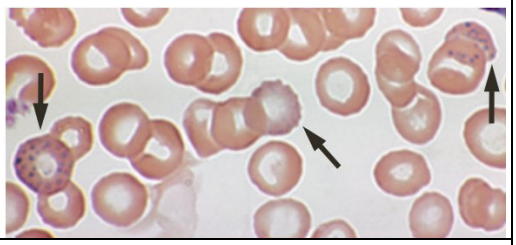
HIGH SUSPECION INDEX NEEDED

HISTORY

➡ *Occupational history & identification lead sources of intoxication*

PBS

➡ *Microcytic + Basophilic stippling (frequently seen but not specific for lead intoxication)*



Lead Intoxication
Source: Herbert & Hendrick

CONFIRMATION

➡ *Elevated blood lead level*

TREATMENT

MAIN THERAPY

- *Remove potential sources of exposure & occupational shift could be needed*

IF HIGHER LEVEL

- *Consider chelation therapy*

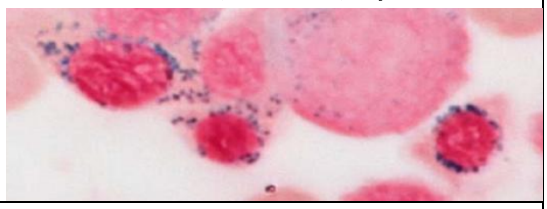
OUTCOME

- *Anemia usually resolves with reduction of lead levels decrease but neuropsychiatric changes may persist*

SIDEROBLASTIC ANEMIA
(CYTOPLASMIC MATURATION DEFECT)

PATHOLOGY

➡ *Due to disruption of heme synthesis & mitochondrial function → characterized by ring sideroblasts → due to the perinuclear accumulation of mitochondrial iron in immature (nucleated) erythroblasts on the bone marrow aspirate smear (by Prussian blue stain)*



Ring Sideroblast
Source: Tomskii JA

CAUSES

CONGENITAL

➡ *Bone marrow failure to produce normal RBCs → instead produce sideroblasts*

ACQUIRED

HEMATOLOGY

➡ *Myelodysplastic syndrome (other causes need to be excluded first)*

ALCOHOL

➡ *25–30% with excessive alcohol use*

COPPER DEFICIENCY

➡ *Due to zinc ingestion/intoxication*

COPPER DEFICIENCY	WILSON DISEASE
Low serum copper & ceruloplasmin levels	
Neutropenia *No Kayser-Fleischer rings*	*No neutropenia* *Kayser-Fleischer rings* *High urinary copper excretion*

LEAD POISONING

➡ *No sideroblasts found*

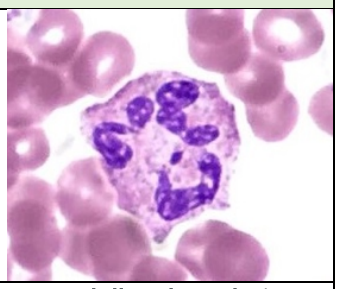
MEDICATIONS

1. *Isoniazid*
2. *Linezolid*
3. *Chloramphenicol*

TREATMENT

➡ *Removal of the offending agent in acquired causes*

<table>
<tr><td rowspan="4">PRESENTATION

NEUROPSYCHIATRIC SYMPTOMS OCCURS IN BOTH VITAMIN B12 & FOLATE DEFICIENCIES BUT MORE COMMONLY WITH VITAMIN B_{12} DEFICIENCY</td><td>BLOOD</td><td colspan="3">1. Macrocytic anemia (B_{12} deficiency can present without anemia but with serious neuropsychiatric symptoms)
2. Pancytopenia
3. Mild unconjugated hyperbilirubinemia (due to continuous low-level intramedullary hemolysis)
4. Lemon-Yellow skin due to skin pallor + Jaundice</td></tr>
<tr><td>GI</td><td colspan="3">1. Weight loss
2. Atrophic glossitis (classic symptom)
3. Diarrhea
4. Oral ulcers only with folate deficiency</td></tr>
<tr><td>NEURO</td><td colspan="3">• Loss of vibratory sense
• Loss of proprioception (& other dorsal column symptoms)
• Spastic ataxia</td></tr>
<tr><td>PSYCHIATRY</td><td colspan="3">➡ Megaloblastic mania –
• Frank psychosis • Hallucination • Dementia</td></tr>
<tr><td colspan="5">DIAGNOSIS</td></tr>
<tr><td rowspan="2">IN BOTH</td><td>PBS</td><td colspan="3">➡ Oval macrocytes & hypersegmented neutrophils
➡ Pancytopenia due to ineffective hematopoiesis
➡ ↓ Retic count
Megaloblastic Anemia
Source: Ed Uthman
  </td></tr>
<tr><td>OTHERS</td><td colspan="3">➡ Blood markers reflect ineffective erythropoiesis causing intramedullary hemolysis –
• ↑ Lactate dehydrogenase • ↑ Unconjugated bilirubin • ↓ Haptoglobin levels</td></tr>
<tr><td rowspan="7">VITAMIN B_{12} DEFICIENCY</td><td rowspan="3">VIT B_{12} BLOOD LEVEL</td><td><200 pg/mL</td><td colspan="2">➡ Diagnostic (95% sensitive)</td></tr>
<tr><td>200–300 pg/mL</td><td colspan="2">= Borderline Low → check Methylmalonic acid (MMA) & homocysteine (HC) – both elevated</td></tr>
<tr><td>>300 pg/mL</td><td colspan="2">➡ Normal = exclude vitamin B_{12} deficiency</td></tr>
<tr><td rowspan="4">Dx PERNICIOUS ANEMIA</td><td>POSITIVE IF AUTOAB</td><td colspan="2">➡ Supports the diagnosis (only 70% sensitivity)</td></tr>
<tr><td rowspan="3">IF NEGATIVE INTRINSIC FACTOR AUTOAB</td><td colspan="2">➡ If clinically considered → check both serum gastrin & pepsinogen levels</td></tr>
<tr><td>Gastrin Level</td><td>↑</td></tr>
<tr><td>Pepsinogen I Level</td><td>↓</td></tr>
<tr><td>Ratio Of Pepsinogen I To Pepsinogen II</td><td>↓</td></tr>
<tr><td>SCHILLING TEST</td><td colspan="2">➡ Using oral radiolabeled B_{12} – not recommended anymore</td></tr>
<tr><td>FOLATE DEFICIENCY</td><td colspan="4">1. Low folate level (but it could be unreliable normal as one meal can correct the folate level)
2. Elevated homocysteine (HC) with >90% sensitivity & specificity in case of suspected folate deficiency despite normal folate level</td></tr>
<tr><td rowspan="3">DDx</td><td colspan="2"></td><td>VITAMIN B_{12} DEFICIENCY</td><td>FOLATE DEFICIENCY</td></tr>
<tr><td colspan="2">Homocysteine Levels</td><td>↑</td><td>↑</td></tr>
<tr><td colspan="2">Methylmalonic Acid Levels</td><td>↑</td><td>Normal</td></tr>
</table>

PRESENTATION		
IN HbSS DISEASE (SCD)		
RENAL	➡ *Recurrent renal microinfarcts → isosthenuria = inability to concentrate urine*	
SPLENIC	➡ *Recurrent splenic infarcts → functional asplenia with increased risk of infection from encapsulated organisms –* • *St.pneumoniae* • *N. meningitidis* • *H. influenzae* • *Salmonella*	
GALLBLADDER	➡ *Bilirubin gallstones due to chromic hemolysis*	
PARVOVIRUS B19	➡ *Parvovirus B19 infection in SCD → decrease erythropoiesis →* 1. *Worsening anemia* 2. *Pure red cell aplasia*	
VASO-OCCLUSIVE PAIN (HALLMARK OF SCD)	**CHARACTER**	➡ *Deep & aching*
	SEVERITY	➡ *Mild to debilitating*
	DURATION	➡ *Hours to days*
	LOCATION	• *Long bones* • *Back* • *Chest* • *Abdomen*
	CO-ASSOCIATED	➡ *Mild redness – warmth – tenderness & low-grade fever*
	PROGNOSIS	➡ *Associated with morbidity & mortality in SCD with inverse relation between the number of painful events & the life expectancy*
CHRONIC PAIN	➡ *Self-reported pain in most of days for >6 months in single or multiple location* ➡ *Idiopathic or due to certain cause as avascular necrosis* ➡ *Exacerbated by emotional stress – anxiety/depression – insomnia*	
ACUTE CHEST SYNDROME (ACS) **CHEST PAIN + HYPOXIA** **LIFE-THREATENING** **THE MAIN CAUSE OF DEATH IN SCD PATIENTS**	**DEFINITION**	➡ *ACS diagnosis = infiltrate on CXR + ≥1 symptom –* • *Fever ≥38.5°C* • *Chest pain* • *>3% ↓ in SpO_2* • *Tachypnea (per age-adjusted normal)* • *Intercostal retractions/Nasal flaring/Accessory respiratory muscles use* • *Cough* • *Wheezing* • *Rales*
	PATHOLOGY	➡ *Vaso-occlusion within the pulmonary microvasculature*
	TRIGGERS	• *Unknown (46%)* • *Infection (29%)* • *Pulmonary infarction* • *Fat embolism*
	SYMPTOMS	➡ *Often follows vaso-occlusive pain episode in the abdomen or bones* • *Chest pain* • *Shortness of breath* • *Rib & sternal pain* • *Arm & leg pain*
	DDx	○ *Pulmonary embolism* ○ *ACS* ○ *Pneumonia*
NEUROLOGY	• *Silent or symptomatic strokes (30% of Hb SS – Hb SC – Sβ⁺-thalassemia)* • *Moyamoya disease (irregular perforating vascular networks near occluded or stenotic vessels in the region corresponding to lenticulostriate & thalamoperforating arteries) predisposing to cerebral bleeding in 3rd & 4th decade of life* • *Lower cognitive function (due to silent ischemia or chronic anemia)*	
THROMBOSIS	• *In situ thrombosis* • *Thromboembolism* • *Fat or bone marrow embolism*	
COMPLICATIONS	➡ *Long-term SCD complications –* 1. *Avascular necrosis of the femoral head* 2. *Pulmonary hypertension* 3. *Sickle retinopathy* 4. *Sickle nephropathy*	
IN OTHER SICKLE CELL SYNDROMES		
SC TRAIT	**Typically**	➡ *Asymptomatic*
	If Symptomatic	➡ *Papillary necrosis with painless hematuria & isosthenuria*
HbSC	➡ *Similar presentation of SS disease but less severe* 1. *As the spleen does not always undergo early autoinfarction (as in HbSS disease) → splenic sequestration is much more likely in HbSC (consider in adult SC patients with tender spleen & worsening anemia)* 2. *Common retinal pathology* 3. *Fat embolism is common*	
COMBINED DISEASES	➡ *Variable clinical presentation*	

GLUCOSE-6-PHOSPHATE DEHYDROGNASE (G6PD) DEFICIENCY

THE MOST COMMON RBCs ENZYME DISORDER

PATHOLOGY

➡ *G6PD deficiency → affecting the hexose-monophosphate (HMP) shunt → causing failure to generate nicotinamide adenine dinucleotide phosphate (NADPH) = essential cofactor in glutathione metabolism (forming reduced glutathione that act as intracellular reducing agent that protect RBCs from oxidative stress)*

➡ *Without NADPH → hemoglobin is prone to oxidation →*

- *Heinz bodies = aggregation of denatured hemoglobin (visible on supravital stain)*
- *Bite cells = trapped erythrocytes that partially destroyed in the spleen (visible in PBS)*

GENETICS

➡ *X-linked G6PD gene (>200 million affected worldwide) so –*

1. *Primarily affects men (only 1 X-chromosome) → 100% of his RBCs are affected*
2. *In women –*
   - *Homozygous involvement through lyonization (inactivation of one of the two X chromosomes) → 50% of her RBCs are affected*
   - *Women with Turner syndrome (XO karyotype)*

DISTRIBUTION

➡ *As there is survival benefit of G6PD against Plasmodium falciparum → so more common in certain descent as –*

- *African*
- *Asian*
- *Mediterranean*
- *Middle Eastern*

VARIANTS

G6PD A	➡ *Variant with mild (often asymptomatic) disease*
G6PD MEDITERRANEAN	➡ *Associated with favism (hemolysis after eating fava beans)*

CAUSES

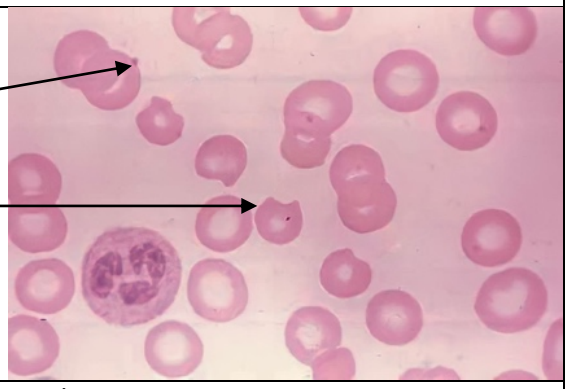
➡ *Common oxidative stressors –*

1. *Infections*
2. *Diabetic ketoacidosis*
3. *Fava beans*
4. *Medications –*
   - *Antimalarials (chloroquine)*
   - *Rasburicase*
   - *Dapsone*
   - *Nitrofurantoin*
   - *Sulfa drugs*
   - *Phenazopyridine*

PRESENTATION

➡ *Mild to massive hemolysis (typically 1 - 3 days after exposure to oxidative stress)*

DIAGNOSIS

G6PD LEVEL	➡ *Normal during acute hemolytic event (false-negative) as the old RBCs destroyed & leaving younger RBCs (that has higher G6PD) so → if clinically suspected → check G6PD levels 2–3 months after the hemolytic event*
G6PD FUNCTION	➡ *Semiquantitative assays that evaluate reduction of NADP to NADPH*
PBS	 **G6PD Deficiency** *Source: Michael Gibson*
DAT	➡ *Rule out autoimmune hemolytic anemia*

TREATMENT

PREVENTION	➡ *Avoiding known triggers (as fava beans)*
ACUTE EVENT	➡ *Eliminate offending agent + Supportive care*

EXTRINSIC SURVIVAL DEFECTS

IMMUNE-MEDIATED HEMOLYSIS

WARM AUTOIMMUNE HEMOLYTIC ANEMIA (WAIHA)	COLD AGGLUTININ DISEASE
PATHOLOGY	
Pathogenic IgG antibodies recognize Rh-type antigens on RBCs surface (with or without complement fixation) → • *Complete phagocytized by macrophages (mainly in spleen) via Fc receptor & removed from the circulation* • *Partial phagocytized → forming spherocytes on PBS*	*Pathogenic IgM antibodies against erythrocyte glycoprotein antigens (I or i antigen) with binding ability depends on the thermal amplitude & complement fixation (mainly in temperature close to body temperature) → if complement fixation occurs →* *hepatic Kupffer cells clear c3-coated RBCs and eliminated from the circulation* ➡ *Agglutination occurs due to autoantibodies span RBCs → causing ↑ MCV (vascular occlusion & organ ischemia can occur rarely due to significant agglutination in severe cases)*
TEMPERATURE FOR OPTIMAL ANTIBODY BINDING TO ERYTHROCYTES	
37.0 °C (98.6 °F) = body temperature	*>37.0 °C (98.6 °F) = below body temperature*
CAUSES	
PRIMARY (IDIOPATHIC)	
SECONDARY	
1. *Autoimmune* 2. *Lymphoproliferative disorders –* • *Chronic lymphocytic leukemia* • *B-cell non-Hodgkin lymphomas* 3. *Drug-induced –* • *Penicillins* • *Cephalosporins* • *NSAIDs* • *Isoniazid* • *Procainamide* • *Methyldopa* • *Levodopa*	1. *Infectious (Mycoplasma & Epstein-Barr virus)* 2. *Lymphoproliferative disorders –* • *IgM MGUS* • *Waldenström macroglobulinemia* • *Other B-cell non-Hodgkin lymphomas*
PRESENTATION	
• *Anemia* • *Fatigue* • *Dyspnea* • *Jaundice* • *Splenomegaly*	• *Anemia* • *Fatigue* • *Dyspnea* • *Jaundice* • *Splenomegaly* • *Acrocyanosis*
PATTERN OF ANTIGLOBULIN TEST (AGT/COOMBS) ON RBC SURFACE	
IgG positive *C3 positive or negative*	*IgG negative* *C3 positive*
PERIPHERAL BLOOD SMEAR (PBS)	
Spherocytes	*Erythrocyte agglutination*
TREATMENT	
Treatment of underlying condition *Glucocorticoids (1st line therapy) with 2/3 of patient responds to the therapy* *Immunosuppression* *Splenectomy with 70% response (reserved for patient that does not respond or tolerate steroid & immunosuppression)* *Transfusion (for symptomatic patient or severe anemia or significant comorbidities) but challenging to find serocompatible donors due to presence of alloantibodies*	*Treatment of underlying condition* *Avoid cold exposure (warm all infusates)* *Rituximab (with fludarabine or bendamustine)* *Plasmapheresis* *No effect of steroid or splenectomy*

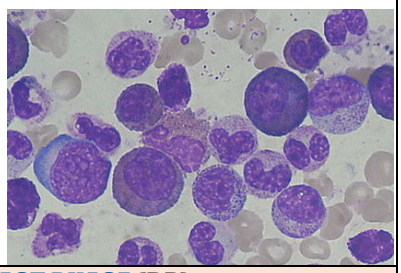
MYELOPROLIFERATIVE NEOPLASMS

MYELOID ELEMENT	MYELOPROLIFERATIVE NEOPLASMS	ACTIVATING MUTATIONS
NEUTROPHIL	Chronic Myeloid Leukemia	• BCR-ABL • CSF3R
MONOCYTE	Myelofibrosis	• JAK2 (50-60%) • Cal-R (35-40%) • MPL (9%)
ERYTHROCYTE	Polycythemia Vera	• JAK2 (97%)
PLATELET	Essential Thrombocythemia	• JAK2 (50-60%) • Cal-R (25-35%) • MPL (4%)
EOSINOPHIL	Hypereosinophilic Syndromes Chronic Eosinophilic Leukemia	• FIP1L1-PDGFRA/B
MAST CELL	Systemic Mastocytosis (No longer part of MPN per WHO)	• CKIT D186V (95%)

CHRONIC MYELOID LEUKEMIA (CML)

PATHOLOGY

➡ *Uncontrolled proliferation & production of mature and maturing granulocytes in blood and bone marrow (generally with normal differentiation) due to t(9;22) = reciprocal translocation of ABL gene on chromosomes 9 to the BCR gene on chromosome 22 → causing abnormally short chromosome 22 = Philadelphia (Ph) chromosome (pathognomic) → generating BCR::ABL1 fusion gene → results in constitutive tyrosine kinase activity that drives the cellular production & CML symptoms*



CML
Source: Paulo Henrique

PHASES (BASED ON WHO5)

CHRONIC PHASE (CP)	BLAST PHASE (BP)
<20% myeloblasts	➡ One of the following criteria – 1. ≥20% myeloblasts in blood or bone marrow 2. Myeloid sarcoma 3. ↑ Lymphoblasts in blood or marrow (but undefined threshold)
More indolent course with most patients present in that phase	Considered as Secondary acute myeloid leukemia (AML)
Very responsive to therapy	Lower response to therapy

PRESENTATION

50%	• Of chronic phase are asymptomatic (accidental lab finding of ↑ neutrophil)
CONSTITUTIONAL	• Weight loss • Excessive sweating • Fatigue • Fever
↑ MYELOID POOL	1. Abdominal fullness (splenomegaly due to expanded myeloid pool with organ infiltration with left shoulder referred pain) 2. Lower sternal tenderness (due to expanded bone marrow)
CELL DYSFUNCTION	• Bleeding due to platelet dysfunction
↑ URIC ACID	• Gouty arthritis due to uric acid overproduction

DIAGNOSIS

PBS (PERIPHERAL BLOOD IS AS ACCURATE AS BONE MARROW SAMPLES)	WBCs	1. Neutrophilia with left shift & increase – • Bands • Metamyelocytes • Myelocytes • Promyelocytes • Myeloblasts • ↓ Leukocyte alkaline phosphatase (LAP) score 2. Basophilia 3. Eosinophilia ➡ Consider CML if left shift with basophilia or eosinophilia with no clinical picture of leukemoid reaction (as severe infection)
	OTHERS	• Thrombocytosis • Normocytic anemia
CYTOGENIC TESTING (CONFIRMATION)	➡ Detection of – 1. Philadelphia chromosome (t(9;22)) Or 2. Its products – BCR-ABL fusion messenger RNA or the BCR-ABL protein (tyrosine kinase)	

TREATMENT

➢ MEDICAL THERAPY

TYROSINE KINASE INHIBITORS (TKIs)	**AGENTS**	• *Imatinib* • *Dasatinib* • *Nilotinib* • *Bosutinib* • *Ponatinib*
	ACTION	➡ *Target BCR-ABL oncoprotein & so stop downstream signaling*
	INDICATION	➡ *Excellent long-term control of CML with survival improvement & reduction of HSCT needs*
	SIDE EFFECT	• *Fluid retention* • *Rash* • *QT prolongation* • *Teratogenic* • *Drug-drug interaction*
	MONITORING	➡ *Consider nonadherence or new mutations in case of TKI resistance or evidence of disease progression despite treatment*
HYDROXYUREA	**INDICATION**	➡ *If baseline WBC >100,000 at the time of diagnosis (or systemic manifestation/symptomatic splenomegaly) till receive confirmatory cytogenic result of CML*
INTERFERON-α	**INDICATION**	➡ *Used in pregnancy*

➢ ALLOGENEIC HSCT

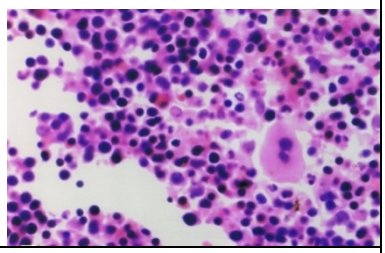
INDICATION	1. *More advanced phases (blast phase or accelerated phase [part of ICC classification but not in WHO5])* 2. *Younger patient with chronic phase + suitable doner + Poor TKI response*
OUTCOME	➡ *HCT is associated with –* 1. *Significant early & late toxicity* 2. *↑ Rate of early mortality*

POLYCYTHEMIA VERA (PV)

PATHOLOGY

➡ *Clonal stem cell disorder with excessive erythrocyte production independent of erythropoietin level*

➡ *JAK2 (Janus Kinase) = Intracellular tyrosine kinase signaling molecule → coupled to cell surface hematopoietic growth factor receptors (erythropoietin receptor)*

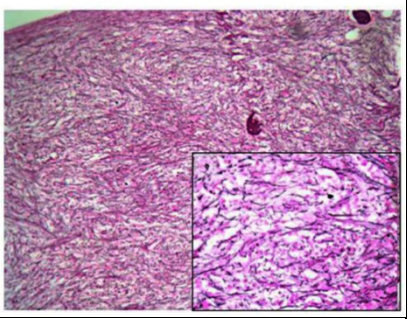
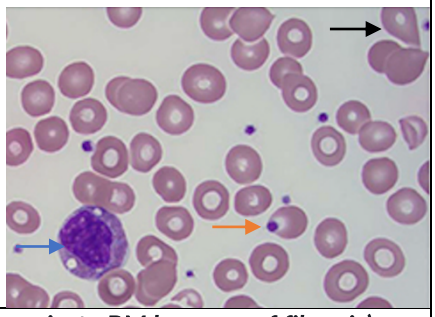


Polycythemia Vera
↑ Erythroid Precursors With Black Condensed Nuclei
Source: Ahmed K.

CAUSES	**PV**	**97%**	• *JAK2 V617F activating mutation*
		3%	• *JAK2 EXON12 mutation*
	2RY POLYCYTHEMIA MORE COMMON	**HYPOXIA**	➡ *Adaptive ↑ erythropoietin in –* • *Sleep apnea* • *Heart failure* • *Smoking/COPD*
		RENAL CANCER	➡ *↑ Erythropoietin production*
		MEDICATIONS	• *Diuretics (relative erythrocytosis due to ↓ plasma volume)* • *Testosterone supplement (stop testosterone or phlebotomy use if Hct >54%)*

PRESENTATION	**ASYMPTOMATIC**	• *Accidental finding in routine complete blood count*
	HYPERVISCOSITY (↑HCT)	• *Headache* • *Fatigue* • *Dizziness* • *Paresthesias*
	CO-ASSOCIATED THROMBOCYTOSIS	• *Erythromelalgia = Triad of Erythema – Warmth – Recurrent burning pain → affecting mostly the extremities*
	↑ HISTAMINE LEVEL	• *Pruritus → after hot bath or shower (aquagenic pruritus)*
	↑ MYELOID POOL	• *Splenomegaly (abdominal fullness/reflux/early satiety)* • *Palpable hepatosplenomegaly with ruddy complexion in some patients*
	RAPID CELLULAR TURNOVER	• *Gout*

PRIMARY MYELOFIBROSIS (PMF)

<table>
<tr><td>PATHOLOGY</td><td colspan="2">
• Clonal stem cell disorder due to proliferation of megakaryocytes → secrete cytokines with transforming growth factor β-1 → causing fibroblast proliferation & deposition of reticulin fibrosis → result in bone marrow fibrosis & impaired hematopoiesis with extramedullary involvement

Myelofibrosis
Bone Marrow Replacement By Reticulin
Source: Chatterjee T.
</td></tr>
<tr><td rowspan="2">CAUSES</td><td>PRIMARY MF</td><td>➡ Mutations of JAK2 – Calreticulin – MPL</td></tr>
<tr><td>SECONDARY MF</td><td>➡ Due to PV & ET progression</td></tr>
<tr><td rowspan="2">PRESENTATION</td><td>CONSTITUTIONAL</td><td>• Fatigue (the most common symptom) • Fever
• Night sweats • Generalized pruritus • Weight loss</td></tr>
<tr><td>SPLENOMEGALY
CHARACTERISTIC</td><td>➡ Common to be massive with presentation of –
• Abdominal fullness • Abdominal pain • Early satiety</td></tr>
<tr><td rowspan="4">DIAGNOSIS</td><td>VARIABLE
PBS</td><td>• ↑ or ↓ Leukocyte count • Anemia • ↑ or ↓ Platelet count
• Eventual pancytopenia as the disease progress
• Leukoerythroblastic blood picture = Circulating Cellular Combination of – Teardrop RBCs (dacrocytes) + Immature RBCs + Immature WBCs

Leukoerythroblastic PBS
• Black Arrow = Teardrop RBC
• Blue Arrow = Immature WBC
• Orange Arrow = Immature Nucleated RBC
Source: Alfath Z</td></tr>
<tr><td>BM BIOPSY
DIAGNOSTIC</td><td>• Dry Tap of bone marrow (due to inability to aspirate BM because of fibrosis) shows extensive fibrosis (exclude miliary TB)
• Strongly positive for the reticulin stain</td></tr>
<tr><td>GENETICS</td><td>• Of BM sample to test for JAK2 (or other mutations in case of negative JAK2)</td></tr>
<tr><td>RISK STRATIFICATION</td><td colspan="2">➡ Using Dynamic International Prognostic Scoring System to determine the overall survival between low & high risk disease</td></tr>
<tr><td rowspan="3">TREATMENT</td><td>ALLOGENIC HSCT</td><td>➡ The only potential curative treatment but carry high morbidity and mortality risks so considered only with patient with enough good condition + features of poor short-term survival –
1. Constitutional symptoms
2. More severe cytopenias
3. ↑ Percentage of blasts in the marrow</td></tr>
<tr><td>JAK1/2 INHIBITOR
• RUXOLITINIB
• FEDRATINIB</td><td>➡ Improve constitutional symptoms in PMF & reduce spleen volume (regardless JAK2 mutation)</td></tr>
<tr><td>SPLENECTOMY</td><td>➡ Avoid due to ↑ morbidity and mortality</td></tr>
</table>

ACUTE LEUKEMIAS

PATHOLOGY

➡ *Clonal disorders of early hematopoietic stem cells → with either early myeloid (acute myeloid leukemia [AML]) or early lymphoid (acute lymphoblastic leukemia [ALL]) lines → producing immature cells (blasts) – myeloblasts or lymphoblasts with lost ability to differentiate while keep replication ability (exceeding 20% of the bone marrow or blood) →*

- *Accumulate in the bone marrow → crowd out normal hematopoietic elements → pancytopenia*
- *Blasts cells spill out into the peripheral circulation*

TYPES

1. *Acute myeloid leukemia (AML) (more common in adults)*
2. *Acute lymphoblastic leukemia (ALL)*

PRESENTATION

➡ *Related to cytopenias –*

1. *Anemia → fatigue & weakness*
2. *Thrombocytopenia → mucosal bleeding*
3. *Neutropenia → infection*

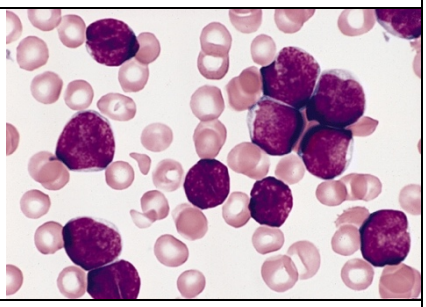
NEUTROPENIC COLITIS (TYPHLITIS)

PATHOLOGY	➡ *After prolonged neutropenia of any cause due to –* 1. *Induction therapy* 2. *Immunosuppressive therapy* 3. *Disease itself*	
ORGANISM	➡ *Gram-negative bacteria*	
PRESENTATION	➡ *Abdominal pain & (sometimes bloody) diarrhea*	
TREATMENT	**ANTIBIOTICS**	• *Piperacillin-tazobactam* • *Cefepime + metronidazole* • *Ceftazidime + metronidazole*
	SURGICAL	➡ *For bowel perforation*

DIAGNOSIS

CONSIDER

➡ *Leukemia if ≥20% blast cells in blood or BM*



Lymphoblast Cells In BM
Source: AFIP

RULE OUT

1. *Leukemoid reaction*
2. *Atypical monocytosis*
3. *Chronic leukemia (overproduction of ≥1 cell line + No blast) & flow cytometry*

DISTINGUISH AML Vs ALL

USING FLOW CYTOMETRY & AUER RODS

AML	ALL
• *Auer Rods are present (pathognomic)* • *Rule out acute promyelocytic leukemia (present with DIC)* • *Stain for myeloperoxidase (MPO) or lysozyme*	• *No Auer Rods* • *Cytogenic abnormalities with B-cell ALL* • *Ph + or Ph –* • *Genetic rearrangement with T-cell ALL* • *Negative for MPO but stain for terminal deoxynucleotidyl transferase (Tdt)*

THERAPY IN PREGNANCY

- *Acute leukemia management during pregnancy is challenging due to the balance between the health benefit of the mother & the baby*
- *There is marked therapy toxicity in the 1st trimester but more tolerated in the 2nd/3rd trimester giving chemotherapy (anthracycline and cytarabine)*

ACUTE MYELOID LEUKEMIA (AML)

PATHOLOGY

➡ *Clonal disorder of the early myeloid cells → overproduction of myeloblasts with decreased production of RBCs – platelets – mature granulocytes → myeloblasts accumulate in –*

- *Peripheral blood*
- *Bone marrow*
- *Lymphoid tissues (rare)*

CAUSES

PRIMARY

➡ *De novo in origin*

SECONDARY
WORSE PROGNOSIS

CHEMICALS

1. *Benzene*
2. *Certain chemotherapy – alkylators & topoisomerase inhibitors*

HEMATOLOGIC DISORDERS

1. *Myeloproliferative disorders*
2. *Myelodysplastic disorders*
3. *Aplastic anemia*
4. *Paroxysmal nocturnal hemoglobinuria (PNH)*

PRESENTATION

CYTOPENIA

- *Anemia → fatigue & weakness*
- *Thrombocytopenia → mucosal bleeding (if platelet count is <20,000/μL)*
- *Functional neutropenia → infection*

BONE/JOINTS

➡ *Bone pain is uncommon in AML (in contrast to ALL)*
➡ *Joint pain (symmetric or migratory) occurs in <5% in AML*

CNS

- *Symptoms of ↑ ICP (headache/lethargy/change of mental status) due to leptomeningeal involvement*
- *Cranial nerves palsy due to involvement of CN III/V/VI/VII*

ORGANOMEGALY

- *Hepatomegaly or splenomegaly in 10% of AML patients = clue of ALL or AML evaluation from prior MPN*
- *Rare lymphadenopathy*

LEUKOSTASIS
MEDICAL EMERGENCY

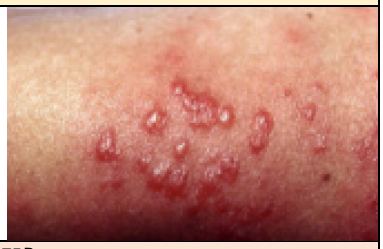
➡ *Increase blood viscosity with >100,000/μL peripheral blood blasts (hyperleukocytosis) → reduce tissue perfusion with end-organ damage as –*

1. *Brain ischemia & hemorrhage (alter mentation)*
2. *Pulmonary vasculature blockage (respiratory distress)*

SWEET SYNDROME

ACUTE FEBRILE NEUTROPHILIC DERMATOSIS

- *Fever*
- *Neutrophilia*
- *Characteristic dense dermal infiltrate*
- *Develop esp. in MDS & MDS evolve into AML*



Sweet Syndrome
Source: Philip R Cohen

SUBSETS

ACUTE PROMYELOCYTIC LEUKEMIA (APML)

PATHOLOGY

- ***Translocation between chromosomes 15 & 17** (including the promyelocytic leukemia gene & retinoic acid receptor α gene) → **expression of the PML-RARα fusion protein → causing physiologic levels of retinoic acid to be ineffective in their innate function to differentiate myeloid blasts → APML***

CRITERIA

- ***Promyelocytes + abundant Auer rods + DIC** (due to release of procoagulants from cytoplasmic granules) – **so diagnosis needs to be made quickly as DIC could be fatal***

DIAGNOSIS

- *Flow cytometry + FISH for t(15;17) – do not delay ATRA therapy for the test results*

AML + t(9;22)

CAUSES

1. *De novo AML or*
2. *Chronic myeloid leukemia (CML) in degenerated blast crisis –*

➡ *Due to presence of Philadelphia chromosome (Ph; BCR-ABL translocation or t(9;22))*

TREATMENT

➡ *Imatinib - tyrosine kinase inhibitor (TKI)*

PLATELET DISORDERS

QUANTITATIVE

THROMBOCYTOPENIA

↓ PRODUCTION	↑ DESTRUCTION
1. *Bone marrow infiltration –* • *Myelofibrosis* • *Metastatic tumors* • *Granulomatous diseases* 2. *Nutritional deficiencies (vitamin B_{12} – folate)* 3. *Stem cell disorder –* • *Aplastic anemia* • *Myelodysplasia* 4. *Liver disease (+ sequestration)*	• *Non-immune mediated thrombocytopenia* • *Immune-mediated thrombocytopenia* • *Heparin-induced thrombocytopenia* • *Thrombotic Thrombocytopenic Purpura* • *Hemolytic uremic syndrome*

QUALITATIVE

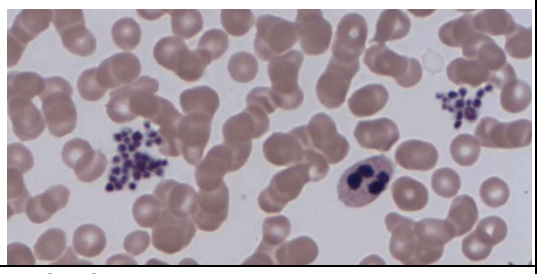
➡ *Qualitative Platelet Disorders –*
1. *Congenital platelet dysfunction*
2. *Acquired platelet dysfunction*

THROMBOCYTOPENIA

CAUSES OF FALSE RESULTS

PLATELET CLUMP

- *Causing Pseudothrombocytopenia due to presence of antibodies to ethylenediaminetetraacetic acid (redraw the blood in citrate or heparin)*



Platelets Clumping
Source: Prof. Erhabor Osaro

↑ COUNT

- *Due to schistocytes that could count as platelets*

↓ COUNT

- *Due to exceptional large platelets that could be counted as RBCs*

PLATELET LEVELS

>100,000/µL	• *Safe level*
>50,000/µL	• *No treatment required & sufficient for surgical procedures (but neurosurgical procedures/operations require 100,000/µL)* • *Sufficient level for anticoagulation*
<50,000/µL	• *Treated before surgeries with significant bleeding risk* • *Anticoagulation required to be stopped*
<10,000/µL	• *Associated with risk of spontaneous bleeding (so transfuse platelet)*

PRESENTATION

1. *Mucocutaneous bleeding –*
   - *Epistaxis*
   - *Hematuria*
   - *Gum bleeding*
   - *Melena*
   - *Menorrhagia*
   - *Hematochezia*
2. *Easy bruising*

EXAMINATION

- *Wet purpura (oral blood blisters)*
- *Petechiae*
- *Ecchymoses*
- *Splenomegaly*

NON–IMMUNE-MEDIATED THROMBOCYTOPENIA

CAUSES

1. *Due to splenomegaly (due to sequestration without destruction) + Associated anemia/leukopenia*
2. *Due to abnormal platelet aggregation (with nonimmune platelet destruction) in –*
   - *Disseminated intravascular coagulation*
   - *Microangiopathic hemolytic anemia (MAHA)*

IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

PATHOLOGY

➡ *Occurs in children & adults → associated with IgG antibodies directed against the 2b/3a glycoproteins on platelets → platelets destruction & hyperfunctional that correlate with low incidence of bleeding (ITP diagnosis requires platelet count to be <100,000/µL)*

TYPES

ACUTE	• *ITP last <3 months*
PERSISTENT	• *ITP last 3–12 months*
CHRONIC	• *ITP last >12 months*

CAUSES

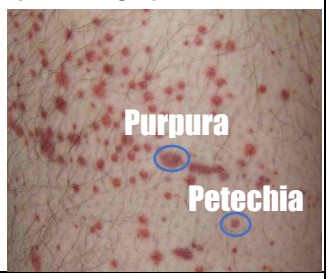
PRIMARY	➡ *Idiopathic*
SECONDARY	• *SLE* • *CLL* • *Pregnancy* • *Drug-induced* • *HIV* • *HCV* • *Helicobacter pylori*

PRESENTATION

➡ *Mainly asymptomatic until ↓ platelet count to <10,000/µL (presentation discussed above)*
➡ *Critical bleeding (intracranial/intraspinal/intramuscular/pericardial) is less common*

EXAMINATION

- *Petechiae*
- *Ecchymoses*
- *No splenomegaly*
- *Nonpalpable purpura (in contrast to palpable IgA vasculitis)*



ITP
Source: Hecktor

DIAGNOSIS

CBC	➡ *Shows only low platelet count*
PBS	➡ *Typically shows few but large (young) platelets + Normal RBCs & WBCs*
CAUTION	• *Repeat the platelet count (as all cases of thrombocytopenia)* • *Rule/out pseudothrombocytopenia*
DIAGNOSIS OF EXCLUSION	➡ *Rule out other causes (HIV/HCV) to diagnose primary ITP*
ANTIPLATELET Ab	➡ *Antiplatelet antibody test is not useful as it is neither sensitive nor nonspecific*
BONE MARROW BIOPSY	➡ *Not needed except to rule out MDS in patients >60 years* ➡ *In ITP → normal marrow cellularity with megakaryocyte hyperplasia*

TREATMENT

STEROID

➡ *Glucocorticoids are indicated as short course of prednisone or dexamethasone (40 mg for 4 days) in asymptomatic newly diagnosed ITP with minor mucocutaneous bleeding & platelet <30,000/µL (can be managed as outpatient)*

SIDE EFFECTS

- *Mood disorders*
- *Insomnia*
- *Fluid retention*
- *Hyperglycemia*
- *Hypertension*

IV IG

➡ *IV Immunoglobulin is used in severe thrombocytopenia & life-threatening bleeding (faster response)*

SIDE EFFECTS

- *Infusion reactions (headache – chills – anaphylaxis)*
- *Renal disease*
- *Thrombosis*

RELAPSE/ REFRACTORY ITP

➡ *2nd-line treatments are indicated –*
1. *Rituximab*
2. *Thrombopoietin receptor agonists (daily oral eltrombopag or avatrombopag or weekly subcutaneous romiplostim) but need to be continuously used to stop relapse*
3. *Splenectomy*

SPLENECTOMY

➡ *Indicated in patients who are unresponsive to or intolerant of medical management (but delay the decision for 1 year after diagnosis due to the possibility of delayed remission)*

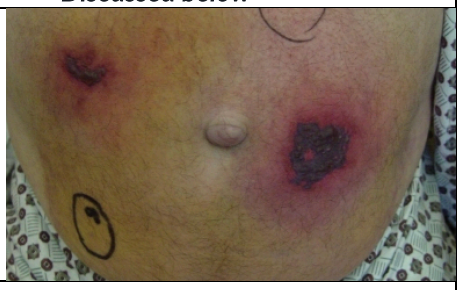
CHRONIC ITP

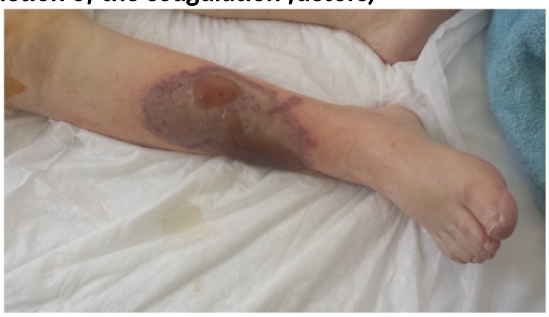
➡ *Therapy decision should balance between the risk of bleeding (as most of chronic ITP patients are asymptomatic) against treatment-related toxicities*

TRANSFUSION

➡ *Platelet transfusion in –*
1. *Severe bleeding*
2. *Prior of invasive procedure*
3. *Critical low platelet count*

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

<table>
<tr><td rowspan="8">TYPES</td><td colspan="2">HIT TYPE I</td><td>HIT TYPE II</td></tr>
<tr><td colspan="3">PATHOLOGY</td></tr>
<tr><td colspan="2">Non–immune-mediated ↓ platelets within 1st few days of exposure to heparin</td><td>Immune-mediated thrombocytopenia within 5 – 10 days after exposure (highest risk with UFH than LMWH) due to antibodies against platelet factor 4 (complexed to heparin)</td></tr>
<tr><td colspan="3">COMPLICATIONS</td></tr>
<tr><td colspan="2">-</td><td>➡ Complicated thrombosis –
• Deep venous thrombosis
• Pulmonary embolism
• Unusual acute arterial occlusions (life threatening)</td></tr>
<tr><td colspan="3">TREATMENT</td></tr>
<tr><td colspan="2">No intervention is needed</td><td>Discussed below</td></tr>
<tr><td>PRESENTATION</td><td colspan="3">• Necrotic skin lesions at heparin injection sites
• VTE manifestation on Heparin (even with normal platelet count)
• Uncommon bleeding presentation
Heparin-Induced Skin Necrosis
Source: Anastasios Katsourakis
  </td></tr>
<tr><td>DDx</td><td colspan="3">➡ HIT + No Heparin Exposure
1. Spontaneous HIT (as HIT)
2. Vaccine-induced immune thrombotic thrombocytopenia (VITT) in case of using adenoviral COVID-19 vaccine</td></tr>
<tr><td rowspan="3">DIAGNOSIS</td><td>CBC</td><td colspan="2">➡ Mainly thrombocytopenia <150,000/µL (but not common to have severe thrombocytopenia)
➡ Caution if patient drops >50% of baseline platelet counts</td></tr>
<tr><td>SCREENING</td><td colspan="2">➡ Using enzyme-linked immunosorbent assay for platelet factor 4 antibodies (PF4) (very sensitive screening test for HIT but not specific)</td></tr>
<tr><td>CONFIRMATION</td><td colspan="2">➡ Either using –
1. Serotonin release assay
2. Heparin-induced platelet aggregation assay</td></tr>
<tr><td rowspan="6">THERAPY TARGETS</td><td>NO HEPARIN</td><td colspan="2">➡ For life</td></tr>
<tr><td>GOAL</td><td colspan="2">➡ Continue to administer the anticoagulant until the platelet count recovers</td></tr>
<tr><td>WARFARIN ONSET</td><td colspan="2">➡ Only when platelet count returns to normal as → warfarin can transiently lower levels of proteins C and S → contribute to clot formation → continue warfarin for at least 3 months</td></tr>
<tr><td>ARGATROBAN/ WARFARIN</td><td colspan="2">➡ As argatroban artificially elevates the INR → goal INR is >4 during argatroban/warfarin overlap → then stop argatroban & continue warfarin</td></tr>
<tr><td rowspan="2">AC THERAPY DURATION</td><td>2-3 Months</td><td>• Without diagnosed thromboembolic events</td></tr>
<tr><td>3-6 Months</td><td>• With diagnosed thromboembolic events</td></tr>
<tr><td>TRANSFUSION</td><td colspan="2">➡ No role for platelet transfusion unless life-threatening bleeding</td></tr>
</table>

<table>
<tr><th colspan="2">PROTEIN C DEFICIENCY</th><th colspan="2">PROTEIN S DEFICIENCY</th></tr>
<tr><td colspan="4">PATHOLOGY</td></tr>
<tr><td colspan="2">Protein C (natural anticoagulant) is vitamin K–dependent protein that degrades activated factors V & VIII</td><td colspan="2">Protein S (natural anticoagulant) is vitamin K–dependent protein that acts as cofactor for protein C that degrades activated factors V & VIII
Circulate as free form or bound to complement-binding protein</td></tr>
<tr><td colspan="4">CAUSES</td></tr>
<tr><td colspan="2">Protein C gene mutations</td><td>CONGENITAL</td><td>Mutations of PROS1 gene</td></tr>
<tr><td colspan="2">Acute thrombosis
DIC
Warfarin therapy
Vitamin K deficiency
Liver disease
Nephrotic syndrome
Protein-losing enteropathy</td><td>ACQUIRED</td><td>➡ As protein C acquired deficiency +
Inflammatory states
HIV
L–asparaginase chemotherapy
Estrogens Conditions –
➡ Contraceptives/ Hormone replacement therapy
➡ Pregnancy/Postpartum state</td></tr>
<tr><td colspan="4">PRESENTATION</td></tr>
<tr><td>HETEROGENEOUS</td><td colspan="3">↑ Pregnancy morbidity
VTE event <50 year old
Strong family history of thrombosis</td></tr>
<tr><td>HOMOZYGOUS (rare)</td><td colspan="3">➡ Neonatal purpura fulminans</td></tr>
<tr><td>WARFARIN-INDUCED SKIN NECROSIS</td><td colspan="3">➡ Due to rapid protein C depletion (before depletion of the coagulation factors)
Warfarin Skin Necrosis
Source: Bakoyiannis C
  </td></tr>
<tr><td colspan="4">DIAGNOSIS</td></tr>
<tr><td colspan="2">Protein C functional testing
(but not testing during VTE event or while on warfarin)</td><td colspan="2">Free form immunoassay</td></tr>
<tr><td colspan="4">TREATMENT</td></tr>
<tr><td colspan="4">Lifetime anticoagulation for unprovoked VTE events</td></tr>
<tr><td colspan="4">METHYLENE TETRAHYDROFOLATE REDUCTASE (MTHFR) GENE POLYMORPHISMS
(No Longer Part Of Standard Hypercoagulable Work-Up)</td></tr>
<tr><td>PATHOLOGY</td><td colspan="3">➡ Causing mild elevations in homocysteine levels → slightly ↑ risk of cardiovascular & thrombotic disease</td></tr>
<tr><td>ETHNICITY</td><td colspan="3">➡ Common in the European ancestry as heterozygous mutation</td></tr>
<tr><td>DIAGNOSIS</td><td colspan="3">1. MTHFR mutation testing
2. Measure homocysteine levels
3. Measure factor VIII levels & plasminogen activator inhibitor activity</td></tr>
</table>

IRON OVERLOAD SYNDROMES

PRIMARY/HEREDITARY HEMOCHROMATOSIS (HH)

PATHOLOGY

➡ *Tissue damage due to abnormal iron deposition due to –*

1. *Hereditary iron hyperabsorption (due to HFE gene mutation) with 3 most common mutations –*
   - *C282Y mutation*
   - *H63D mutation*
   - *S65C mutation*
2. *Secondary to chronic transfusion therapy*

GENETIC EXPRESSION	**80-90%**	• *% Of primary hemochromatosis with homozygosity for C282Y*
	NO IRON OVERLOAD	• *No risk of iron overload in case of isolated H63D or S65C mutations (without C282Y mutation)*
	WOMEN	• *Relative low phenotypic penetrance of HFE mutations*
PRESENTATION	**ASYMPTOMATIC**	➡ *Consider if iron studies (transferrin saturation >45% + ↑ serum ferritin level)* ➡ *Caution with serum ferritin as it is acute-phase reactant (↑in acute or chronic inflammatory conditions/infections/malignancies)*
	ORGAN INJURY	• *Irreversible cirrhosis & cardiomyopathy (major morbidities)* • *Small joint arthritis* • *Endocrinopathies* • *Pituitary injury → androgen insufficiency & excess melanin excretion → skin hyperpigmentation (bronze diabetes)*

DIAGNOSIS

TARGET PATIENTS

Symptomatic patient Or
Asymptomatic patient with ALT/AST >35 U/L Or
Adult 1st Degree Relative Of HH

STEP 1
IRON STUDIES

Serum transferrin saturation (TS)
Serum ferritin (SF)

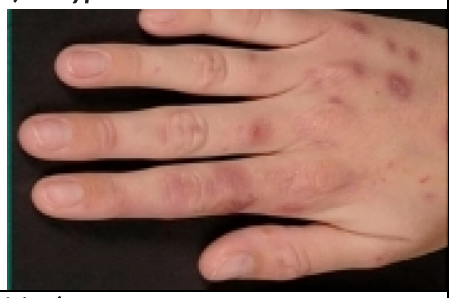
- *TS <45% + Normal SF* → *No Further Evaluation*
- *TS ≥45% &/or ↑ SF* → *HFE Genotype (CONFIRMATORY TEST)*

STEP 2
GENETIC CONFIRMTORY TEST

HFE Genotype (CONFIRMATORY TEST)

- *C282Y/C282Y Homozygous*
  - *SF >1000 ng/ml Or ↑ LFT* → *Liver Biopsy For Fibrosis Staging & Exclude Concurrent Liver Diseases*
  - *SF <1000 ng/ml + Norm LFT* → *Therapeutic Phlebotomy*
- *C282Y/H63D Heterozygote Or C282Y Heterozygote Or Non-C282Y* → *Assess for Other Liver/Hematologic Disorder +/- Liver biopsy/Special* → *↑ Hepatic Iron Conc (HIC) + SF >1000 ng/ml* → *Therapeutic Phlebotomy*

STEP 3
INTERVENTION

<table>
<tr><th colspan="3">TREATMENT</th></tr>
<tr><td>INDICATIONS</td><td>PHLEBOTOMY</td><td>1. C282Y homozygous + serum ferritin level >300 ng/mL in men & >200 ng/mL in women & transferrin saturation ≥45% (based on 2019 American College of Gastroenterology guideline)
2. Symptomatic patients with evidence of end-organ injury
3. Patient with more significantly elevated serum ferritin level (>1000 ng/mL)</td></tr>
<tr><td rowspan="2">PHLEBOTOMY PROTOCOL</td><td>FREQUENCY</td><td>➡ Initially 1–2 per week (depends on serum ferritin/organ damage/Hct level) → maintaining schedule (once target is achieved) to be 2–6 times per year</td></tr>
<tr><td>TARGET</td><td>➡ Maintain serum ferritin 50–100 ng/mL (1 unit of blood = 450–500 mL contains 200 - 250 mg of iron)</td></tr>
<tr><td>MONITORING</td><td colspan="2">➡ Monitoring ferritin levels at 3 – 6 month intervals</td></tr>
<tr><td>AVOID</td><td colspan="2">➡ Avoid supplemental iron & alcohol</td></tr>
<tr><td>SCREENING</td><td colspan="2">1. First-degree relatives of patients with hereditary hemochromatosis
2. For hepatocellular carcinoma for cirrhotic patients (but likely unnecessary in case of stage 3 fibrosis or less on liver biopsy)</td></tr>
<tr><td>OUTCOME</td><td colspan="2">➡ Normal life expectancy with regular monitoring for patients with no hepatic fibrosis or cardiomyopathy</td></tr>
<tr><th colspan="3">SECONDARY IRON OVERLOAD</th></tr>
<tr><td>CAUSES</td><td colspan="2">1. Patients with chronic transfusions requirement (after 20–25 units of PRBCs = 5 g of iron) –
• Hemoglobinopathies (thalassemias – sickle cell disease)
• Bone marrow failure
• Hematologic malignancies (myelodysplastic syndrome)
2. Porphyria cutanea tarda (PCT) (uncommon)
➡ Acquired abnormalities in porphyrin metabolism
➡ Associated with –
• Underlying liver disease (especially hepatitis C)
• Characteristic criteria – Cutaneous blisters (often on the hands) & Hypertrichosis
 
PCT
Source: H Jorn Bovenschen</td></tr>
<tr><td>COMPLICATION</td><td colspan="2">➡ The same end-organ involvement as in HH (esp. hepatic deposition)</td></tr>
<tr><td>TREATMENT</td><td colspan="2">➡ No indication for therapeutic phlebotomy due to underlying anemia in these patients (except porphyria cutanea tarda with well response to phlebotomy)
➡ Main treatment is iron chelation therapy –
1. Parenteral deferoxamine or
2. Oral deferasirox & deferiprone</td></tr>
</table>

MULTIPLE MYELOMA (MM)

PATHOLOGY

➡ *B-cell neoplasm → clonal expansion of plasma cells (evolves from asymptomatic premalignant stage of clonal plasma cell proliferation of monoclonal gammopathy of undetermined significance [MGUS]) → produce monoclonal (M) protein or paraprotein of any Ig (IgG/IgA/IgD/IgE/IgM) subclasses (but mostly IgG kappa) in forms –*

1. *Intact immunoglobulin or*
2. *Ig fragments of heavy or*
3. *Ig fragments of light chains*

➡ *Can present as –*

- *Smoldering (asymptomatic) disease with higher risk of clonal plasma cell burden than MGUS & higher risk of transformation to MM requiring therapy*
- *Symptomatic disease (immediate treatment is required to prevent complications)*

PRESENTATION

C – HYPERCALCEMIA

➡ *>11 mg/dL or >1 mg/dL higher than the upper limit of normal*
➡ *Due to ↑ bone resorption (along with renal dysfunction)*

R – RENAL FAILURE

➡ *>2 mg/dL or creatinine clearance <40 mL/min*
➡ *Due to –*

1. *↑ FLCs causing cast nephropathy = myeloma kidney (due to FLCs deposition in the distal tubules → tubulointerstitial damage [type 2 (proximal) renal tubular acidosis])*
2. *Hypercalcemia*
3. *Other causes –*

- *Immunoglobulin light-chain amyloidosis*
- *Cryoglobulinemic glomerulonephritis*
- *Proximal tubulopathy*

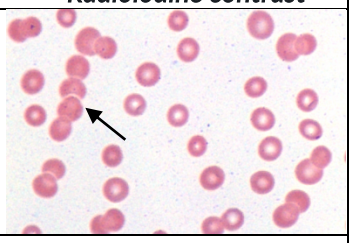
➡ *Patients with cast nephropathy are prone to more renal injury (even with normal baseline creatinine level) due to –*

- *Dehydration*
- *NSAID*
- *Radioiodine contrast*

A – ANEMIA

➡ *Hemoglobin <10 g/dL or 2 g/dL below the lower limit of normal*
➡ *Commonly normocytic anemia with rouleaux formation in MM (therapy is indicated) due to –*

1. *Bone marrow plasma cell infiltration*
2. *Renal disease*

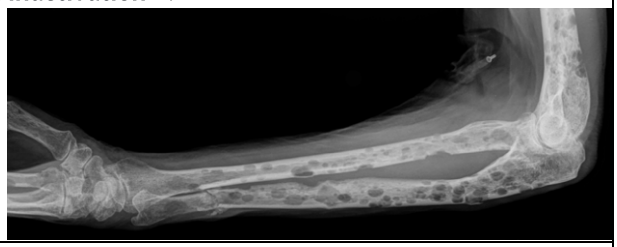


Rouleaux Formation
Source: Gabriel Caponetti

B – BONE PAIN (MOST COMMON) (Back & Ribs)

➡ *≥1 lytic bone lesions on imaging studies*
➡ *Due to osteoclast activation & osteoblast inactivation →*

1. *Development of lytic lesions*
2. *Vertebral body compression fracture*
3. *Prone to pathologic fractures with minimal or no trauma*



Punched-Out Lytic Lesions
Source: Hellerhoff

EXTRAMEDULLARY PLASMACYTOMA (PLASMA CELL TUMORS)

➡ *Causing –*

- *Fatigue*
- *Weight loss*
- *Local symptoms (based on location) – spinal cord compression & neuropathy/radiculopathy*

HYPERVISCOSITY

➡ *Headache (association with immunoglobulin M [IgM] MM >5 g/dL)*

↑ INFECTION RISK

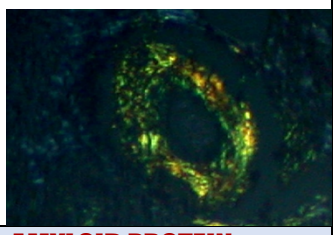
➡ *↑ Risk of respiratory infections due to –*

1. *Leukopenia*
2. *Lymphocyte dysfunction*
3. *Hypogammaglobulinemia (despite ↑ total immunoglobulin but normal immunoglobulins ↓)*

IMMUNOGLOBULIN LIGHT-CHAIN AMYLOIDOSIS

PATHOLOGY

- *Disorders associated with extracellular deposition of low-molecular-weight proteins in β-pleated sheet configuration that circulate in the blood & deposit in various organs*
- *All amyloid deposits shows characteristic apple-green birefringence under polarized light microscopy of the tissue with Congo red staining*



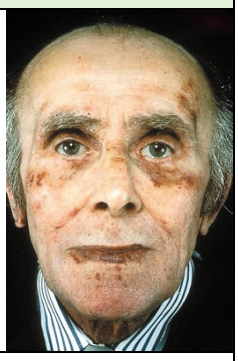
Gastric Amyloidosis
Source: Ed Uthman

TYPES	ASSOCIATED CONDITION	AMYLOID PROTEIN
AL IMMUNOGLOBULIN LIGHT-CHAIN AMYLOIDOSIS **MOST COMMON**	• *Plasma cell dyscrasias (MGUS/MM)* • *Waldenström macroglobulinemia (rare)*	*Monoclonal free λ or κ light chains (FLCs) that deposit in –* • *Heart* • *Kidneys* • *Skin* • *Liver* • *Other organs*
AGE-RELATED (SENILE) AMYLOIDOSIS **2nd MOST COMMON**	*Aging (account for 10% of heart failure with preserved ejection fraction)*	*Wild-type or variant transthyretin amyloid (TTR)*
AA AMYLOID A (SECONDARY) AMYLOIDOSIS	1. *Rheumatoid arthritis* 2. *Inflammatory bowel disease* 3. *Familial Mediterranean fever* 4. *Chronic infection*	*Serum amyloid A protein*
HEREDITARY AMYLOIDOSIS	*Inherited*	*Mutated TTR* *Fibrinogen α chain*
DIALYSIS-RELATED AMYLOIDOSIS	*Any case of dialysis*	*β_2-microglobulin*

AL AMYLOIDOSIS PRESENTATION

SKIN (30-40%)

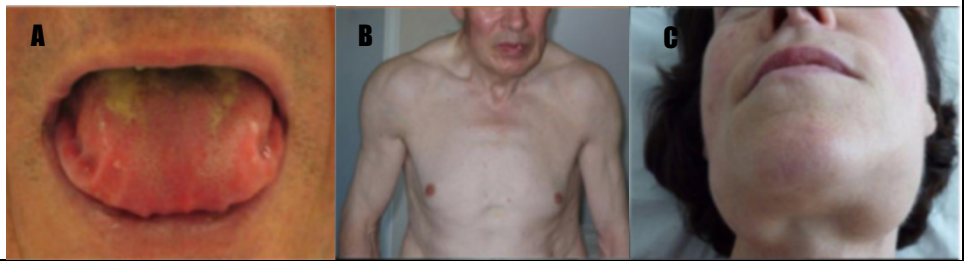
- *Generalized waxy appearance*
- *Easy bruising with minor pressure (Pinch Purpura)*
- *Periorbital violaceous discoloration (Periorbital Purpura = Raccoon Eyes)*
- *Yellow waxy papules & plaques (esp. in the periorbital location)*
- *Dystrophic nails*



Raccoon Eyes In Amyloidosis
Source: Prof. P N Hawkins

MUSCULOSKELETAL

- *Macroglossia (A)*
- *Muscle pseudohypertrophy (periarticular soft tissue and muscle infiltration on MRI) (B)*
- *Submandibular gland enlargement (C)*
- *Symmetric arthropathy (joint space widening on plain radiographs)*
- *Carpal tunnel syndrome (impaired median nerve conduction across the carpal tunnel)*



Amyloidosis
Source: Estelle Desport

ONCOLOGIC EPIDEMIOLOGY

MOST COMMON CANCER (IN U.S.)	In Men	In Women
1st	Prostate cancer	Breast cancer
2nd	Lung cancer	
3rd	Colorectal cancer	

MOST COMMON CAUSES OF CANCER DEATHS (IN U.S.)	In Men	In Women
1st	Lung cancer	
2nd	Prostate cancer	Breast cancer
3rd	Colorectal cancer	Pancreas cancer

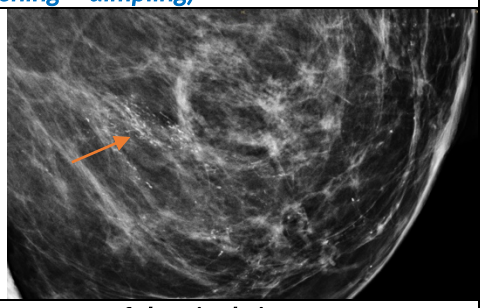
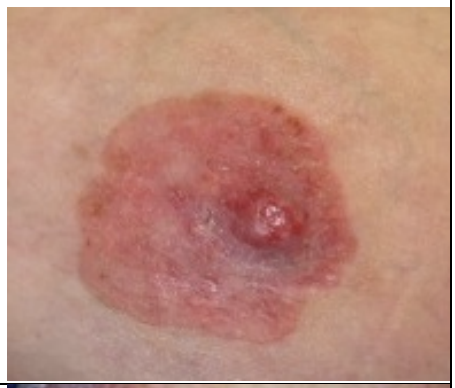
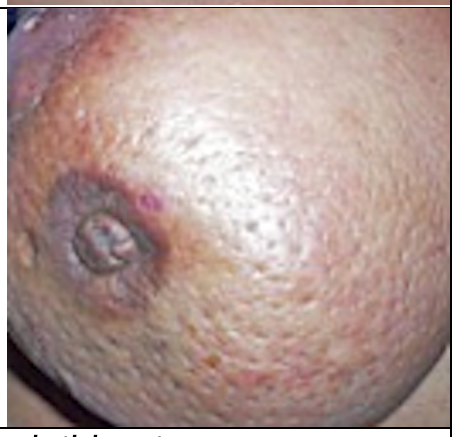
BREAST CANCER

RISK FACTORS

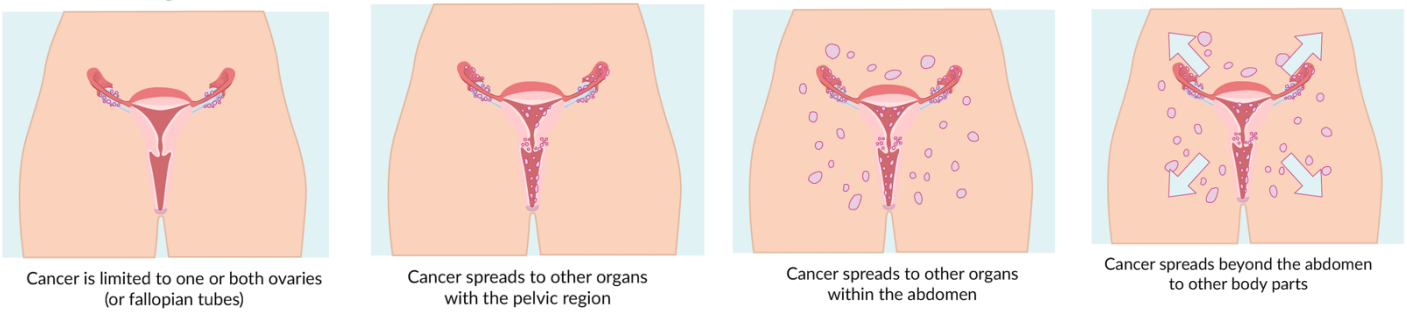
PERSONAL Hx	1. *Female sex (100-fold higher than men)* 2. *Higher incidence in non-Hispanic white and black women* 3. *↑ With aging with median age of diagnosis of 61 year old*
PMH	1. *Prior breast cancer* 2. *Prior breast biopsy* 3. *Chest radiation exposure for Hodgkin lymphoma (30–50% risk of breast cancer)*
FHx	➡ *Breast cancer in one or more 1st degree relative (esp. premenopausal and/or bilateral breast cancer)*
LIFESTYLE	• *Alcohol use* • *Obesity (BMI ≥30)* • *Lack of physical exercise*
OBGY Hx	1. *Early menarche* 2. *Nulliparity* 3. *Late 1st pregnancy (after 30 years old)*
MEDICATIONS	➡ *Postmenopausal combined estrogen + progesterone hormone replacement therapy* ➡ *Postmenopausal estrogen replacement therapy (ERT) –* 1. *Increase the risk of breast cancer (& endometrial cancer) after 5 years of use* 2. *In 1998 Heart and Estrogen/Progestin Replacement Study (HERS) trial –* ➡ *ERT is associated with increased risk of secondary cardiac events in the 1st year of treatment & no cardiovascular benefit at the 7-year follow-up* 3. *Long-term ERT therapy → associated with ↑ risk of thromboembolism & biliary tract surgery*
GENETICS	➡ *Inherited genetic mutations (BRCA1 & BRCA2) = 5–10% of all breast cancers with 45–75% lifetime risk of breast cancer*
BREAST FINDINGS	1. *Atypical ductal hyperplasia in breast biopsy → 4× normal risk* 2. *DCIS or LCIS (ductal/lobular carcinoma in situ) → 10× normal risk* 3. *↑ Breast density*

GENETIC PATHOLOGY OF BREAST CANCER

In Women	BRCA 1 (1st IDENTIFIED BREAST CANCER GENE)	BRCA 2
	BRCA1 or BRCA2 genes mutations → account for 30–50% of all inherited breast cancer	
	ASSOCIATED DISEASES	
	1. *Breast cancer (50–85% lifetime risk compared to 12% in the general population)* 2. *Ovarian cancer (40% lifetime risk compared to 1.5% in the general population) (most cases of familial ovarian cancer)* 3. *Colorectal cancer* 4. *Prostate cancer*	1. *Breast cancer (high risk)* 2. *Ovarian cancer (10–20% risk)* 3. *Melanoma* 4. *Pancreatic cancer* 5. *Prostate cancer*
In Men	➡ *Breast cancer is rare (<1% of all breast cancer diagnoses)* ➡ *BRCA mutations → causes increased risk for breast cancer (especially BRCA2)* ➡ *Male carriers → 6% lifetime risk of breast cancer (compared to <0.1% in the general male population)*	

<table>
<tr><th colspan="3">PRESENTATION</th></tr>
<tr><td rowspan="5">TYPICAL</td><td>ONSET</td><td>➡ Incidental findings or via mammogram</td></tr>
<tr><td>CONSISTENCY</td><td>➡ Hard</td></tr>
<tr><td>MOBILITY</td><td>➡ Fixed</td></tr>
<tr><td>BORDERS</td><td>➡ Well-defined dominant mass with irregular borders</td></tr>
<tr><td>LOCAL ADVANCEMENT</td><td>1. Fixation to surrounding tissue
2. Palpable axillary or supraclavicular lymphadenopathy
3. Skin findings (erythema – thickening – dimpling)</td></tr>
<tr><td>DUCTAL CARCINOMA IN SITU (DCIS)</td><td colspan="2">➡ Noninvasive breast cancer that presents as –
• Usually as calcifications on mammography
• Less commonly as palpable mass or with Paget disease of the breast
• ↑ Incidence from 3% of breast cancers to 20% – 25% of breast cancers (due to the implementation of mammography)
Microcalcification In DCIS
Source: JMArchn
  </td></tr>
<tr><td>PAGET DISEASE</td><td colspan="2">➡ Rare form of breast cancer that present as asymmetric eczema of the nipple in non-breastfeeding woman with persistent unilateral oozing from the nipple → mostly with underlying ductal breast cancer with or without palpable mass
DDx
➡ The most common acute areolar eczema rah is contact dermatitis or allergic eczema (consider Paget disease if there is no response to treatment)
DIAGNOSIS
➡ Skin biopsy or scrape cytology + Diagnostic breast imaging (MRI is indicated if no imaging abnormalities are detected to evaluate for occult disease)
TREATMENT
➡ Breast-conserving therapy (based on the extent of disease) + Nipple-areolar resection in all patients
Paget Disease Of The Breast
Source: Lily Chu
  </td></tr>
<tr><td>INFLAMMATORY BREAST CANCER
(VERY AGGRESSIVE WITH POOR PROGNOSIS)</td><td colspan="2">➡ Presents as –
• Mastitis with warmth – redness – swelling (note that mastitis in nonlactating woman is rare)
• Erythema involving at least 1/3 of breast skin
• Peau d'orange (skin of the orange) appearance
• Nipple retraction
Inflammatory Breast Cancer
Source: Schairer C
  </td></tr>
<tr><td rowspan="5">NIPPLE DISCHARGES</td><td>LESS LIKELY TO BE CANCER</td><td>➡ If discharge occurs from both breasts</td></tr>
<tr><td>ABNORMAL NIPPLE DISCHARGE</td><td>➡ Not milky & bilateral</td></tr>
<tr><td>GREENISH DISCHARGE</td><td>➡ Draining cyst</td></tr>
<tr><td>BLOODY DISCHARGE</td><td>➡ Due to papilloma & could be a sign of cancer</td></tr>
<tr><td>CLEAR DISCHARGE</td><td>➡ Other presentation of breast cancer</td></tr>
</table>

STAGING	STAGE	CRITERIA
	STAGE I DISEASE (FAVORABLE)	• Cancer in one or both ovaries • Not high grade or clear cell • Negative peritoneal washings • No rupture
	STAGE I DISEASE (UNFAVORABLE)	➡ Confined to ovaries but with – • High-grade or clear cell histology • Rupture • Positive peritoneal washings
	STAGE II DISEASE	➡ Spread beyond ovaries but confined to pelvis
	OPTIMALLY DEBULKED STAGE III DISEASE	➡ Spread to abdomen + Residual tumor masses <1 cm after debulking surgery
	SUBOPTIMALLY DEBULKED STAGE III	➡ Spread to abdomen + Residual masses >1 cm after debulking surgery
	STAGE IV DISEASE	➡ Spread beyond abdomen (distant metastases)



PREVENTION	➡ Prophylactic bilateral salpingo-oophorectomy recommended in women with BRCA1/BRCA2 or MMR gene mutations (after completion of childbearing)		
PRESENTATION	➡ Usually the presentation is at advanced stage with – • Constipation • Bloating • Abdominal/pelvic pain • Early satiety		
PROGNOSIS	FAVORABLE FACTORS	• Early stage • Low grade • Serous histology • Young age • Extent of disease after surgical debulking (volume of residual disease after surgery correlates inversely with survival)	
	5-YEAR SURVIVAL RATE	I	➡ 89 %
		II	➡ 71 %
		III	➡ 41 %
		IV	➡ 20 %
	OUTCOME	➡ 31% of ovarian cancer patients survive 10 years (1/3 of these long-term survivors have stage III or IV)	
TREATMENT	STAGING PROCEDURES	• Total hysterectomy • Bilateral salpingo-oophorectomy • Peritoneal washings • Omentectomy • Pelvic & para-aortic lymph node sampling	
	STAGE I	• Surgical resection only if favorable disease • Add 3 – 6 chemotherapy cycles (carboplatin & paclitaxel) if unfavorable disease	
	STAGE II	➡ Surgical resection + 3 – 6 cycles of chemotherapy (carboplatin & paclitaxel)	
	STAGE III	OPTIMALLY DEBULKED	➡ Surgery followed by IV or IV/Intraperitoneal chemotherapy + Maintenance olaparib after first-line chemotherapy
		SUBOPTIMALLY DEBULKED	➡ Surgery (improves survival) + Chemotherapy (including neoadjuvant (preoperative) chemotherapy to shrink unresectable cancer + Maintenance olaparib after first-line chemotherapy
	STAGE IV	➡ As Stage III Suboptimally debulked disease	

DIAGNOSIS

PSA	**↑ PSA**	➡ *Consider diagnosis of prostate cancer with ↑ serum prostate-specific antigen (PSA)*
	CONFIRM	➡ *Repeat PSA at least 1 month later (+ Urology referral with persistent elevation or abnormal prostate finding on digital rectal examination [DRE])*
PROSTATE BIOPSY	**METHOD**	➡ *Using transrectal ultrasonography + 5–7 cores per side (establish sufficient diagnostic yield)*
	HIGH RISK RESULT	• *Atypical small acinar proliferation* • *Multifocal high-grade prostatic intraepithelial neoplasia*
	SIDE EFFECTS	1. *Anxiety* 2. *Physical discomfort* 3. *Bleeding* 4. *Urinary obstruction* 5. *Infection* 6. *Mortality (0.2%)*
GENETICS	➡ *Perform genetic testing for BRCA gene mutation in all men with high-risk disease (also if there positive lymph nodes or metastatic disease [11.8% mutation risk in metastatic disease])*	
IMAGING	➡ *Obtain imaging studies to assess for regional lymph node involvement and metastatic disease (not indicated for very low or low risk patients)*	
STAGING	1. *Bone scan + Either CT or MRI of the pelvis (as bone & LNs are the most likely sites of metastasis)* 2. *Lymph nodes samples at time of surgery*	

RISK STRATIFICATION

	VERY LOW/LOW	INTERMEDIATE	HIGH	VERY HIGH
TNM SCORING	*T1/T2a*	*T2b-T2c*	*T3a*	*T3b-T4*
PSA	*<10 ng/mL*	*10–20 ng/mL*	*>20 ng/mL*	-
GLEASON SCORE	*Gleason 3+3 (Grade Group 1)*	*Gleason score 7 (Grade Group 2–3)*	*Gleason score 8–10 (Grade Group 4–5)*	*Primary Gleason pattern 5*
BIOPSY	-	-	-	*>4 cores with Grade Group 4–5*

TNM SCORING

➢ TUMOR (T)

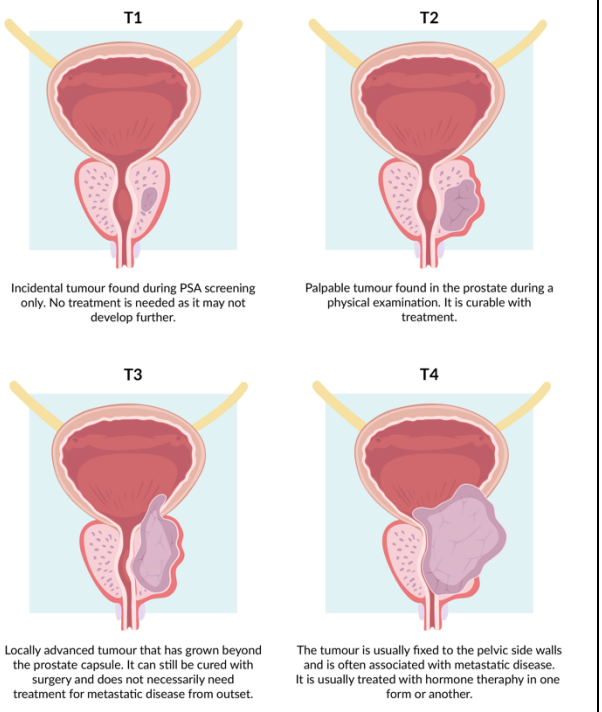
T1	➡ *Tumors are not palpable or seen by imaging but accidently discovered in pathologic resected benign sample*	
	T1a	➡ *<5% of sample*
	T1b	➡ *>5% of sample*
T2	➡ *Tumors are palpable*	
	T2a	➡ *Involves <50% of one lobe*
	T2b	➡ *Involves >50% of one lobe*
	T2c	➡ *Involve both lobes of the prostate*
T3	**T3a**	➡ *Tumors extend through the prostate capsule*
	T3b	➡ *Tumors involves the seminal vesicles*
T4	➡ *Tumors spread to other structures other than seminal vesicles as urinary bladder or pelvic wall*	

➢ LYMPH NODES (N)

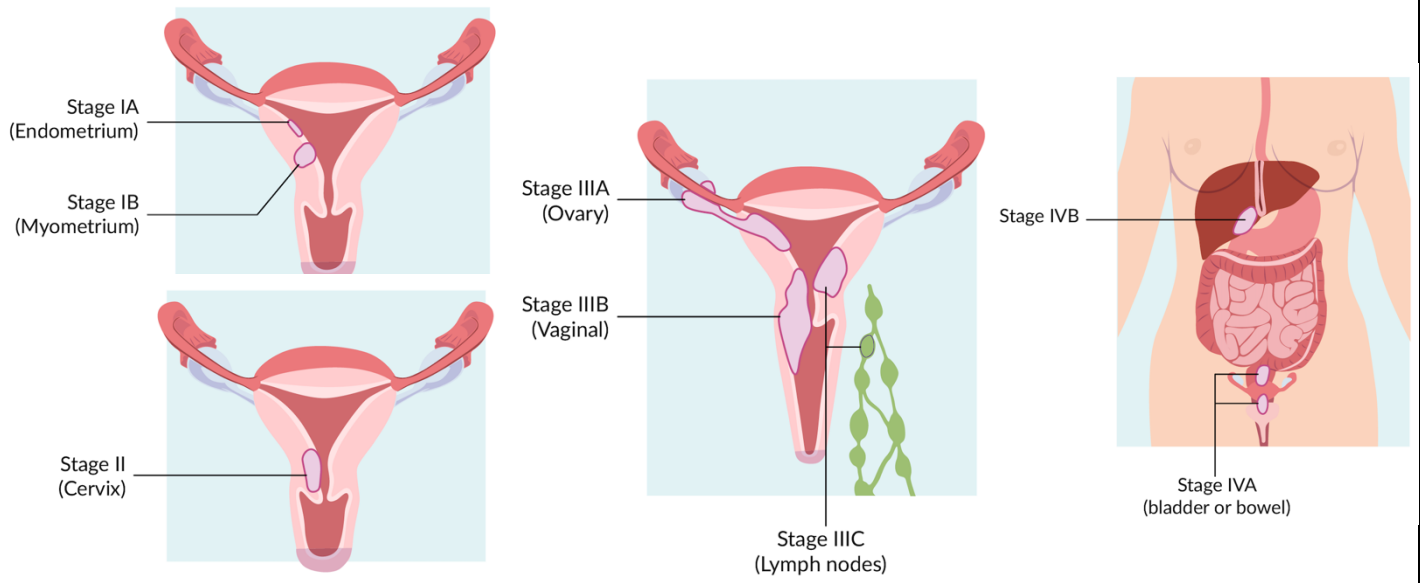
Nx	➡ *Nearby LNs are not evaluated*
N0	➡ *No cancer cells found in nearby LNs*
N1	➡ *Cancer cells are found in nearby LNs*

➢ METASTASIS (M)

M0	➡ *Cancer has not spread beyond prostate*	
M1	➡ *Cancer has spread beyond prostate*	
	M1a	• *Cancer has spread to distant LNs*
	M1b	• *Cancer has spread to bone*
	M1c	• *Cancer has spread to other organ (with or without bone)*



STAGING	BASED ON FIGO SYSTEM (NOT AJCC'S TNM CLASSIFICATION)		
	STAGE I	➡ *Tumor is confined to the uterus*	
		IA	➡ *Tumor extends to <1/2 of myometrium*
		IB	➡ *>1/2 of myometrium*
	STAGE II	➡ *The tumor extends to the cervical stroma*	
	STAGE III	IIIA	➡ *Tumor invades by direct extension to the vagina*
		IIIB	➡ *Tumor invades by direct extension to the ovaries*
		IIIC	➡ *Tumor invades by direct extension to the pelvic or paraaortic nodes*
	STAGE IV	IVA	➡ *Tumor invades the bladder or bowel*
		IVB	➡ *Metastatic beyond the true pelvis*



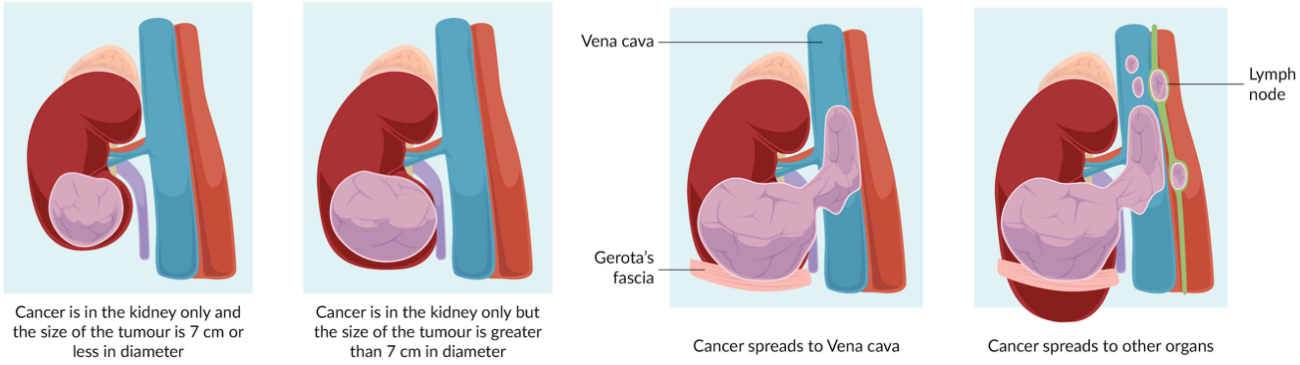
TREATMENT		
	EARLY STAGE + HIGH RISK ENDOMETRIAL CANCER	➡ *Total hysterectomy with bilateral salpingo-oophorectomy + Adjuvant chemotherapy (prevent relapse)*
	EARLY STAGE + NO HIGH RISK ENDOMETRIAL CANCER	➡ *Total hysterectomy with bilateral salpingo-oophorectomy + Either observation or postoperative adjuvant radiation*
	HIGH RISK CRITERIA OF ENDOMETRIAL CANCER	1. *Grade 2–3 endometrioid histology* 2. *Invasion of the outer 1/2 of the myometrium* 3. *Invasion of the lymphatic space or vasculature*
	HIGH RISK DETERMINATION	≥70 YEARS OF AGE: ➡ *Only 1 risk factor is required*
		51–69 YEARS OF AGE: ➡ *2 risk factors are required*
		≤50 YEARS OF AGE: ➡ *All 3 risk factors are required*

VULVAR CANCER

(4TH MOST COMMON GYNECOLOGIC CANCER IN U.S.)

TYPES	➡ *Squamous cell cancer (the most common)*
RISK FACTORS	1. *Vulvar or cervical intraepithelial neoplasia* 2. *Smoking* 3. *Vulvar lichen sclerosus* 4. *Immunodeficiency syndromes*
PRESENTATION	➡ *As vulvar lesion with bleeding or pruritus*
DIAGNOSIS	➡ *Mostly diagnosed at early stage*
TREATMENT	➡ *Radical surgical resection*
PROGNOSIS	➡ *Favorable with 5-year survival rate >70%*

SCREENING	➡ *Consider screening high risk (as genetic factors) patients with CT or U/S to diagnose early disease*	
STAGING	**TNM CLASSIFICATION**	
	➢ **TUMOR (T)**	
	T1	➡ *Tumors are confined to within the kidney and limited to ≤7 cm*
	T2	➡ *Tumors are confined to within the kidney but >7 cm*
	T3	➡ *Tumors extend outside the kidney (to the perinephric tissues or the renal vein) but not past the Gerota (renal) fascia or into the ipsilateral adrenal gland*
	T4	➡ *Tumors invade past the Gerota fascia or into the ipsilateral adrenal gland*
	➢ **LYMPH NODES (N)**	
	N0	➡ *No regional lymph nodes metastasis*
	N1	➡ *Metastasis regional lymph nodes*
	➢ **METASTASIS (M)**	
	M0	➡ *No distant metastasis*
	M1	➡ *Distant metastasis*
	PROGNOSTIC STAGING GROUPS	
	I	• *T1 + N0 + M0*
	II	• *T2 + N0 + M0*
	III	• *T1-3 + N1 + M0*
	IV	• *T4 + Any N + M0* • *T4 + Any N + M1*



TREATMENT	
LOCALIZED MASS	1. *Surgery is the primary treatment (Radical nephrectomy or Partial if small mass <4 cm)* 2. *Cryoablation or Radiofrequency ablation used in older patient with multiple comorbidities* ➡ *No role for adjuvant therapy (no survival benefit with risk of toxicity)*
LOCOREGIONAL MASS	➡ *Radical nephrectomy + 1 year of Pembrolizumab (especially if high risk of recurrence)*
METASTATIC DISEASE	➡ *Debulking of the primary cancer (in selected patients) + Either or combined –* 1. *Pembrolizumab (immune checkpoint inhibitors) Or* 2. *Tyrosine kinase inhibitors (axitinib) Or* 3. *Interleukin-2*
BRAIN METASTASIS	➡ *Surgical resection or preferred radiation therapy (stereotactic radiosurgery) before starting systemic therapy (immunotherapy &/or vascular endothelial growth factor [VEGF] inhibitors)*
RADIATION THERAPY INDICATIONS	1. *Painful bone metastases* 2. *Brain metastases* 3. *Painful recurrences in the renal bed*
POSTOPERATIVE SURVEILLANCE	➡ *Detect recurrent disease with –* • *Periodic visit (based on the extent of local disease)* • *Basic laboratory studies* • *Chest & abdomen imaging*

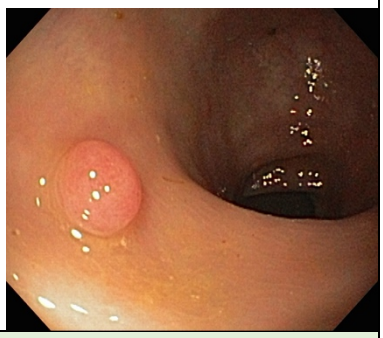
COLORECTAL CANCER (CRC)

THE 3RD MOST COMMON CANCER & 2ND LEADING CAUSE OF CANCER DEATH IN NORTH AMERICA

EPIDEMIOLOGY

LIFETIME RISK	**4.5%**	• *In men*
	4.1%	• *In women*
INCIDENCE	➡ ↓ *Incidence and mortality due to risk factors changes (as reduced smoking) & early detection*	
90%	➡ *Survival rates are >90% with localized disease (emphasizing the importance of early detection)*	

3 CANCER MECHANISMS

CHROMOSOMAL INSTABILITY **MOST COMMON** **85%**	• *Due to abnormal cells that gain or lose whole or large fractions of chromosomes (aneuploidy) at ↑ rate compared with normal cells → progression of normal colon to adenoma to cancer* • *Most commonly mutated gene is the adenomatous polyposis coli (APC) gene = multifunctional tumor suppressor gene* • *Germline mutations in APC → familial adenomatous polyposis*
MICROSATELLITE INSTABILITY (MSI) **15%**	• *Due to mismatched bases at repeated DNA microsatellites (microsatellites = dozens to hundreds of repetitive nucleotide sequences throughout the human genome) → defective DNA mismatch repair (deficient mismatch repair [dMMR]) → leading to multiple mutations → adenomas & cancer* 1. *Lynch syndrome (autosomal dominant with germline mutation in mismatch repair gene including MLH1/MSH2/MSH6/PMS2)* 2. *Epithelial cell adhesion molecule gene (EPCAM)* 3. *Sporadic methylation of MLH1 promoter*
HYPERMETHYLATION OF TUMOR SUPPRESSOR GENES	• *Causing serrated lesions (characterize by sawtooth histology appearance that usually found in proximal colon with flat morphology that makes it difficult to distinguish from normal mucosa) & cancer* **Sessile Serrated Adenoma** *Source: Samir* 

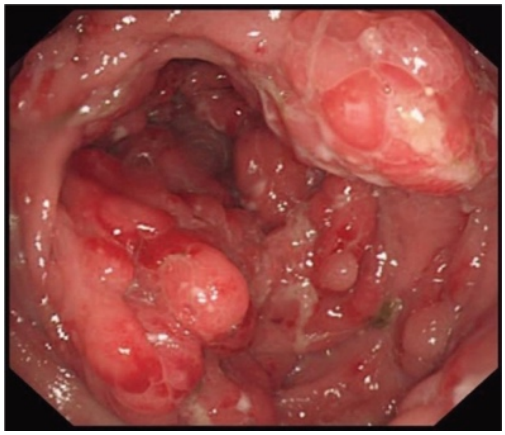
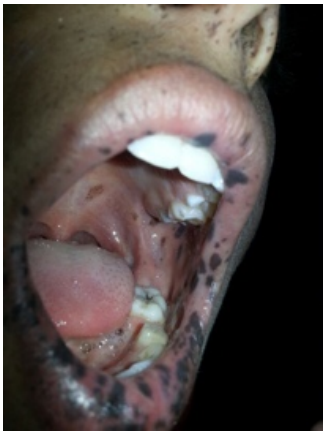
RISK FACTORS

➢ NON-MODIFIABLE RISK FACTORS

DEMOGRAPHICS	• *≥45 years of age* • *Male sex* • *Personal or family Hx of colon adenomas or cancer (2x risk if family history of colorectal cancer in 1st-degree relative)*
GI	• *Long-standing (≥8 years) of IBD (Ulcerative colitis/Crohn colitis) with 2.7x increased risk* • *History of childhood abdominal radiation*
GENETICS	1. *Familial polyposis syndromes* 2. *Lynch syndrome (LS)* 3. *BRCA1 mutation*
UROLOGY	• *Ureterocolic anastomoses after bladder surgery*

➢ MODIFIABLE RISK FACTORS

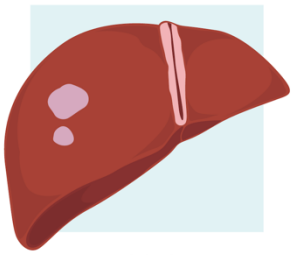
DIET	• *High in high in red & processed meat* • *Low fruits/vegetables/fiber/dairy*
LIFESTYLE	1. *Sedentary lifestyle* 2. *Obesity* 3. *Alcohol & tobacco use*
COMORBIDITY	➡ *Diabetes mellitus type 2*

➢ **POLYMERASE PROOFREADING–ASSOCIATED POLYPOSIS**	
CAUSE	• *Due to mutations in polymerase proofreading genes POLE & POLD1* • *Tumor testing shows microsatellite instability*
PATHOLOGY	➡ *Combine features of both FAP & Lynch syndrome + Endometrial cancer*
HAMARTOMATOUS POLYPOSIS SYNDROMES	
➢ **PEUTZ-JEGHERS SYNDROME**	
CAUSE	➡ *Due to mutations in the STK11 (LKB1) gene*
CANCER RISK	➡ *No cancer risk as hamartomas but they have the risk of developing adenoma that turns to carcinoma* ➡ *Risk of cancer is 50% by 60 years of age*
PATHOLOGY	1. *Multiple hamartomatous polyps throughout small intestine (primarily) + colon (occasionally) + rectum + stomach* 2. *Melanotic pigmentation (freckles) on the lips & buccal mucosa*  **Colonic Polyps** *Source: Ye Zong MD*  **Peutz-Jeghers Syndrome** *Source: Abdullah Sarhan*
PRESENTATION	➡ *Most commonly – abdominal pain due to intussusception or bowel obstruction due to large polyp* ➡ *Bleeding*
SCREENING	➡ *Perform upper gastrointestinal endoscopy (esophagogastroduodenoscopy) + video capsule endoscopy (VCE) + colonoscopy between the ages of 8–10 years with repeated screening based on on the findings at baseline examination*
➢ **JUVENILE POLYPOSIS SYNDROME (JPS)**	
CAUSE	➡ *Due to mutations in the BMPR1A & SMAD4 genes*
PATHOLOGY	➡ *Multiple juvenile hamartomas polyps (>5 polyps) in –* • *Colon (98%)* • *Stomach (14%)* • *Small bowel (14%)*
PRESENTATION	➡ *18.5 years is the average age at JPS diagnosis* ➡ *Rectal bleeding (most common)*
SCREENING	➡ *Colonoscopy every 1–3 years at age 12 or sooner if symptomatic*
➢ **PTEN HAMARTOMA SYNDROME (COWDEN SYNDROME)**	
CAUSE	➡ *Due to germline mutations in the tumor suppressor gene PTEN*
PRESENTATION	1. *Macrocephaly* 2. *Characteristic benign skin findings –* • *Facial trichilemmomas* • *Lipomas* • *Oral papillomas*

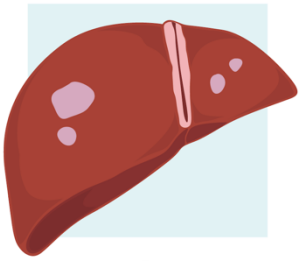
STAGING & TREATMENT

BARCELONA CLINICAL LIVER CANCER (BCLC) STAGING SYSTEM

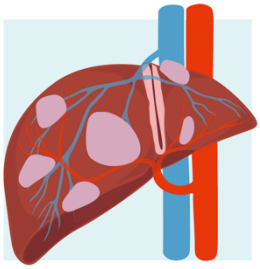
	DESCRIPTION	TREATMENT
STAGE 0 (VERY EARLY)	*Single small tumor (<2 cm) with good liver function & performance status (Child-Pugh A & Eastern Cooperative Oncology Group [ECOG] 0)*	*Surgical resection or liver transplantation*
STAGE A (EARLY)	*Single tumor >2 cm Or up to 3 tumors <3 cm with good liver function & performance status*	*Surgical resection* *Radiofrequency or microwave ablation for lesions ≤3 cm* *Targeted radioembolization for lesions >3 cm* *Liver transplantation*
STAGE B (INTERMEDIATE)	*Multiple tumors in the liver with still good liver function and performance status*	*Transarterial chemoembolization (TACE)*
STAGE C (ADVANCED)	*Cancer spread to blood vessels/lymph nodes/other organs Or poor performance status*	*Palliative options as systemic therapy with Immune checkpoint inhibitor (atezolizumab) + Anti-angiogenic agent (bevacizumab)*
STAGE D (END-STAGE)	*Severe liver damage or poor performance status (ECOG 3–4) (often with significant symptoms)*	*Palliative care is the main treatment*
FOLLOW-UP	➡ *Surveillance for HCC recurrence after surgical resection using contrast-enhanced multiphasic CT or MRI every 3 – 6 months*	



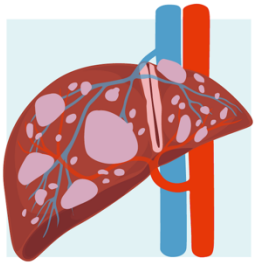
Very early/early stage BCLC 0, A



Intermediate stage BCLC B



Advanced stage BCLC C



Terminal stage BCLC D

ESOPHAGEAL CANCER

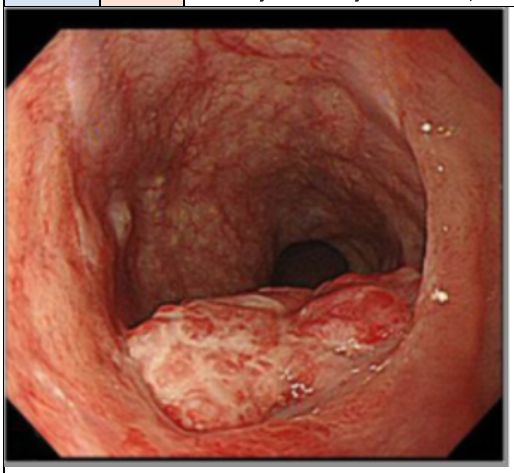
INCIDENCE	**GEOGRAPHY**	➡ *High-prevalence areas are Asia/southern/eastern Africa*	
	TYPES	**PROXIMAL ESOPHAGUS**	• *Squamous cell carcinoma (90%) worldwide but incidence has been decreasing*
		DISTAL ESOPHAGUS	• *Adenocarcinoma incidence has been rising (with involving proximal stomach = gastroesophageal cancer)*
	AGE OF ONSET	➡ *5th to 7th decades of life*	
	GENDER	➡ *3–4x more common in men*	
	15% - 25%	➡ *5-year survival rate based on cancer stage at initial presentation*	

RISK FACTORS	ADENOCARCINOMA	SQUAMOUS CELL CARCINOMA
	• *Male sex* • *Older age* • *GERD* • *Barrett esophagus* • *Obesity* • *Tobacco use*	• *Tobacco & alcohol use (major causes)* • *Achalasia* • *Poor socioeconomic status* • *Prior thoracic radiation* • *Caustic injury* • *Poor oral hygiene* • *Nitrosamine exposure* • *Human papillomavirus infection* • *Nutritional deficiencies (zinc – selenium)* • *Nonepidermolytic palmoplantar keratoderma (AD disorder associated with yellow wax-like hyperkeratosis on the palms & soles [tylosis])*

PRESENTATION	• *Dysphagia with solid foods (most common)* • *Anemia (due to gastrointestinal bleeding)* • *Weight loss* • *Anorexia* • *Chest pain*	
DIAGNOSIS	**DIAGNOSTIC TEST**	➡ *Upper endoscopy with biopsy*
	STAGING TESTINGS	• *Endoscopic ultrasonography to assess the depth of tumor penetration & lymph nodes involvement (for locoregional disease)* • *PET/CT imaging (for metastatic disease)*

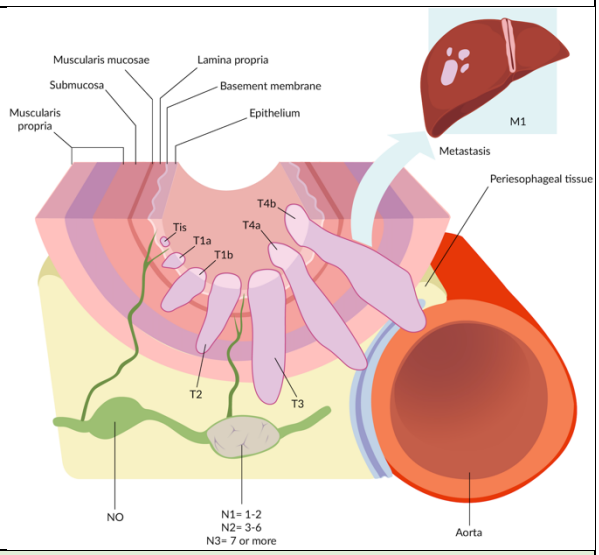
CLINICAL TNM STAGING

0	➡ *Tis (carcinoma in situ) + N0 + M0*	
I	• *T1 (tumor invades the lamina propria/muscularis mucosae or submucosa) + N0 Or N1 (metastases in 1 or 2 regional LNs) + M0*	
II	• *T2 (Tumor invades the muscularis propria) + N0 Or N1 (metastases in 1 or 2 regional LNs) + M0 Or* • *T3 (Tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures) + N0 + M0*	
III	• *T3 + N1 + M0 Or* • *T1-3 + N2 (metastases in 3-6 regional LNs) + M0*	
IV	**IVA**	• *T4 (Tumor invades adjacent structures) + N0-2 + M0 Or* • *Any T + T3 (metastases in ≥7 regional LNs) + M0*
	IVB	➡ *Any T + Any N + M1 (Distant metastasis)*



Esophageal Cancer

Source: Toshihiro Kitajima



TREATMENT

LOCO-REGIONAL DISEASE	• *Neoadjuvant chemotherapy (improve survival) + Surgical resection (primary line of treatment) + Adjuvant chemotherapy/radiotherapy* • *Adjuvant immunotherapy (PD-1 inhibitors) can be added which is more effective in squamous cell cancers than in adenocarcinomas* ➡ *Endoscopic resection with organ-sparing manner used for superficial tumors limited to the mucosal lining (T1a) with no lymph node metastasis & low-risk features (as in differentiation and lymphovascular invasion)*
UNRESECTBABLE	➡ *Chemoradiation*
RECURRENT/ METASTATIC DISEASE (NOT CURATIVE)	➡ *Based on –* 1. *Histologic type (adenocarcinoma or squamous cell carcinoma)* 2. *Presence & intensity of programmed death ligand 1 (PD-L1)* 3. *If human epidermal growth factor receptor 2 (HER2) is overexpressed (25% of esophageal cancer)* • *Nivolumab or pembrolizumab (immune checkpoint inhibitors) used with chemotherapy for PD-L1 positive cancers* • *Adding trastuzumab (anti-HER2 monoclonal antibody) to chemotherapy and pembrolizumab improves response (if HER2-positive gastroesophageal cancer & PD-L1 positive)*

NODULES FEATURES ON CT SCAN

SIZE

➡ ↑ *Risk of malignancy with ↑ size –*

NODULE SIZE	MALIGNANCY RATE
<5 mm	• <1%
5-9 mm	• 2 - 6%
8-20 mm	• 18%
>20 mm	• >50%

LOBAR LOCATION

➡ *Pulmonary malignant nodules can be found in lung lobes but the nodules found in the upper lobe → increased probability of being malignant*

ATTENUATION

➡ *Provide nodule classification as solid versus subsolid*

GROWTH & STABLE RATE

SOLID NODULE

➡ *Growth = ↑ in size of >2 mm (nodules unchanged for >2 years are benign)*

SUBSOLID NODULE

➡ *Growth =*

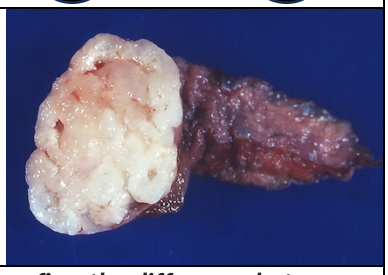
- *↑ Attenuation Or*
- *↑ In the size Or*
- *Solid component development*

CALCIFICATION

MOST LIKELY BENIGN NODULES				MOST LIKELY MALIGNANT NODULES	
POPCORN	LAMINATED	CENTRAL	DIFFUSE	PUNCTATE	ECCENTRIC

FAT CONTENT

➡ *Presence of fat within smoothed border lung nodule = reliable presumption of pulmonary hamartoma*



Hamartoma
Source: Yale Rosen

BORDERS

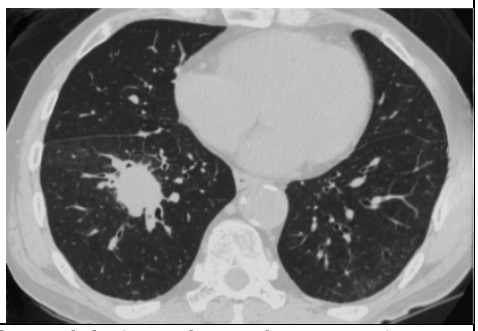
➡ *Nodule border characteristics can suggest the diagnosis but cannot confirm the difference between benign & malignant nodules –*

BENIGN NODULES

- *Well-defined smooth border (but cannot exclude malignancy as up to 20% of lung cancers have smooth margins)*

MALIGNANT NODULES

- *Spiculated (due to malignant cells growth along the pulmonary interstitium = corona radiata sign) but still can be seen with benign lesions*
- *Lobular (due to differential growth rates within nodules)*



Spiculated Nodule
Source: Kodama K

ENHANCEMENT

➡ *Enhancement = subtracting the precontrast attenuation of the nodule from the peak attenuation after contrast (sensitivity 98% - specificity 58% - negative predictive value 96%) –*

- *Malignant nodules enhance >20 Hounsfield Units (HU)*
- *Benign nodules enhance <15 HU*

SKIN CANCER

MELANOMA

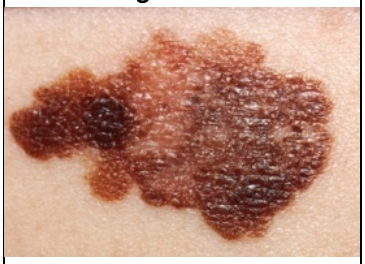
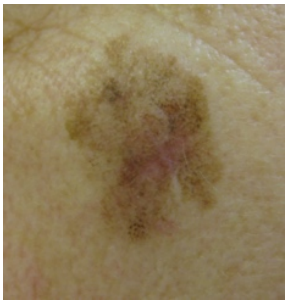
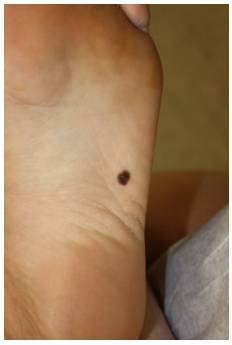
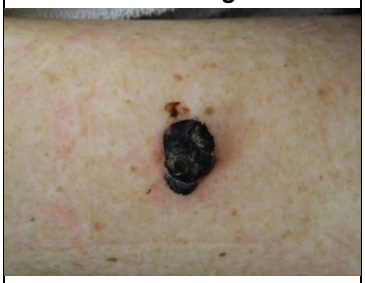
PATHOLOGY

- ➡ *Most melanomas arise de novo (not from preexisting nevus) so → removing all moles does not prevent melanoma development (2017 meta-analysis found only 29% of melanoma patient with pre-existing navi)*
- ➡ *Superficial spreading melanoma is the subtype most likely to be associated with pre-existing nevus*

RISK FACTORS

SKIN TONE	➡ *Fair-skinned & light-haired*
SUN EXPOSURE	➡ *Freckled people with sunlight exposure (especially with childhood severe sunburns)*
NAVI	1. *Many dysplastic nevi* 2. *Many ordinary nevi* 3. *Congenital nevus*
HISTORY	1. *Family history of melanoma (10% of melanoma are familial)* 2. *Prior personal history of melanoma*
IMMUNITY	➡ *Immunosuppression*

4 SUBTYPES

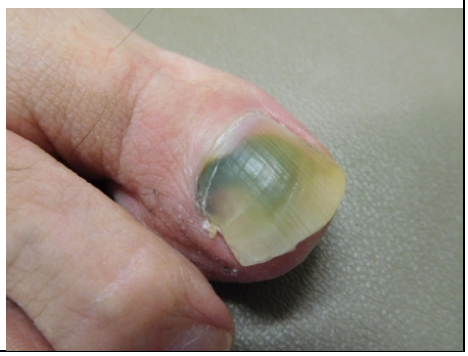
← HORIZONTAL GROWTH →			↓ VERTICAL GROWTH ↓
SUPERFICIAL SPREADING	**LENTIGO MALIGNA**	**ACRAL LENTIGINOUS**	**NODULAR**
The most common (70%) with variable pigmentation & irregular borders	*Tan or brown macules that arise in sun-damaged areas*	• *Palms* • *Nails* • *Soles* • *Mucosa*	*The most aggressive type with early metastasis due to initial vertical growth*
			
Source: OpenStax College	*Source: Kilbad*	*Source: Kelly Nelson*	*Source: DermNetZ*

PRESENTATION

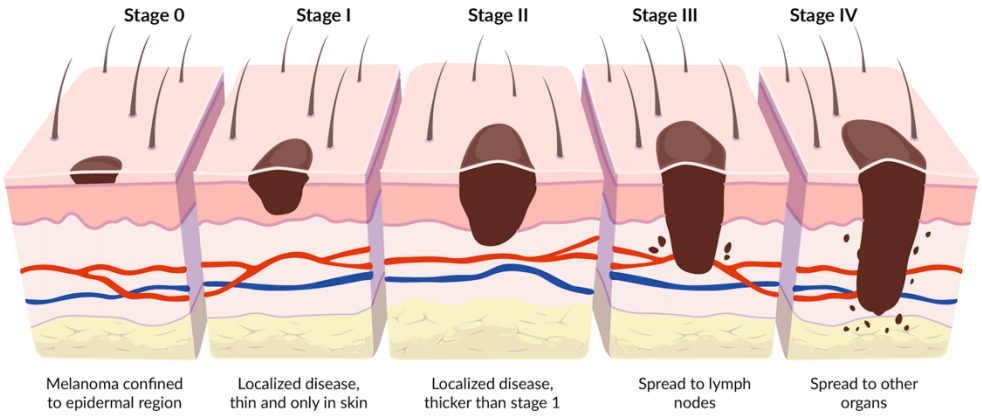
AGE	➡ *Concerning if >50 years old*		
LOCATIONS	**SUPERFICIAL SPREADING SUBTYPE**	**MEN**	➡ *On the backs*
		WOMEN	➡ *On the lower legs*

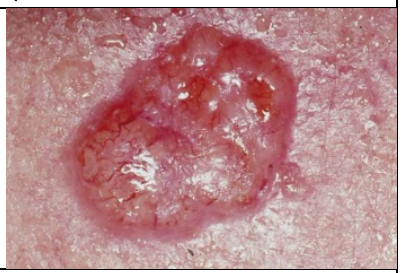
HUTCHINSON NAIL SIGN

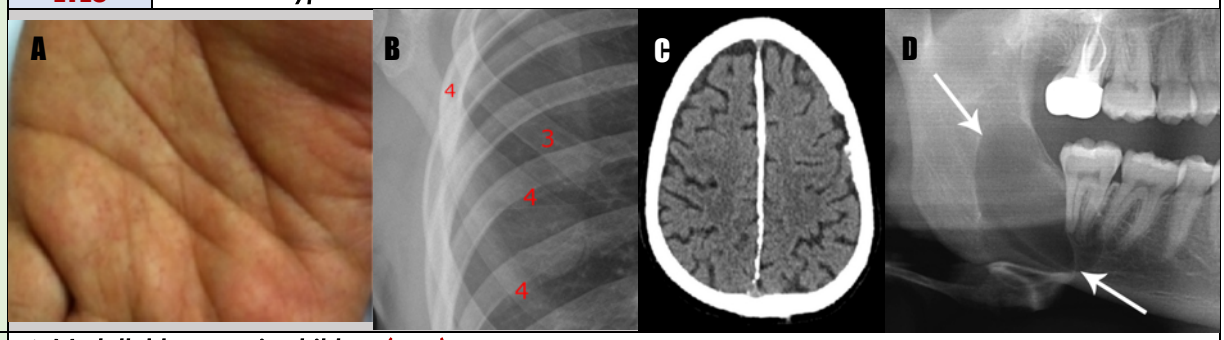
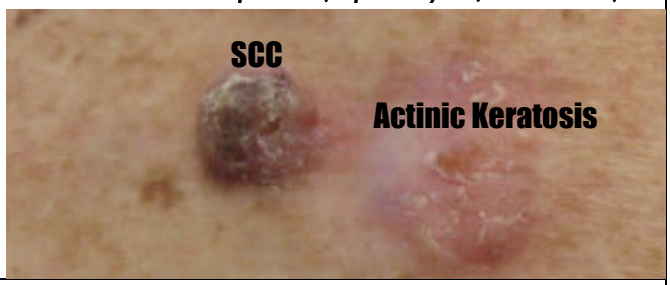
- *Important clinical clue to diagnose subungual melanoma (DDx is subungual hematoma)*
- *Extension of brown or black pigment from the nail bed → to the adjacent cuticle & proximal or lateral nail folds*

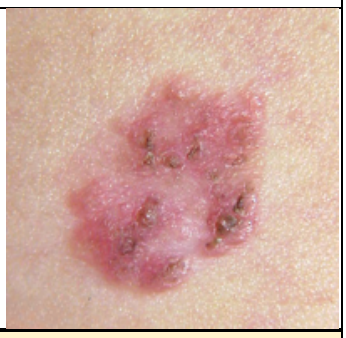


Hutchinson Nail Sign
Source: Nicole C DeMartinis

ASSESSMENT	ASSESSMENT OF THE MALIGNANT MELANOMA POSSIBILITY	
	A	• *Asymmetry*
	B	• *Borders are irregular*
	C	• *Color variation*
	D	• *Diameter >6 mm is suspicious*
	E	• *Evolving lesions are more suspicious*
STAGING	**NEW SYSTEM**	➡ *Based on TNM (Tumor size – Lymph Node Involvement – Metastases) of the American Joint Committee on Cancer's AJCC Cancer Staging Manual (8th Edition)* 
	OLD SYSTEM	➡ *Breslow thickness (based on the depth of the lesion on biopsy)*
DIAGNOSIS	**EXCISIONAL BIOPSY**	➡ *The preferred method that allow for early diagnosis & to improves prognosis and mortality → proper excisional biopsy (saucerization biopsy) of any suspicious lesion with 1–3 mm rim of normal skin & contiguous subdermal fat on the bottom*
	PARTIAL BIOPSY	➡ *Partial incisional biopsy can be acceptable option if the excision of the entire melanoma is not feasible due to –* • *Size (large lesions) or* • *Locations (on face/palm/sole/ears)*
PROGNOSTIC FACTORS	**AGE/SEX**	• *Better prognosis for <50 years of age & female*
	LOCATIONS	• *Improved outcomes – extremities > trunk > head & neck*
	DEPTH	• *Poorer outcome with deeper lesions (most important factor)*
	TUMOR FEATURES	1. *Mitotic index (mutations in the mitogen-activated protein kinase [MAPK] pathway associated with poor prognosis)* 2. *Ulceration*
	METASTASIS	1. *Number of involved regional lymph nodes* 2. *Site of systemic metastases*
	LABS	➡ *↑ LDH levels (important independent prognostic factor with disseminated melanoma) but no longer automatically reflect M1c stage*
	DISTANT RISK	• *Based on –* 1. *Depth of invasion (Breslow depth)* 2. *Ulceration* 3. *Nodal involvement*

TREATMENT		
MMS INDICATIONS	➡ *Mohs Micrographic Surgery (MMS) is indicated in selected cases –* **1.** *Melanoma in situ* **2.** *Lentigo maligna* **3.** *Melanoma of head/neck/hands/feet/pretibia/nails/ankles*	
LOCAL THERAPY	• *For early disease –* ➡ *Wide local excision (WLE) with 1–2 cm margin + Sentinel lymph node biopsy (for thicker melanoma)*	
SYSTEMIC THERAPY	**1.** *Using targeted therapy &/or immunotherapy if sentinel lymph node biopsy is positive (any nodal metastasis is ≥1 mm)* **2.** *Neoadjuvant pembrolizumab (immune checkpoint inhibitor) is indicated before surgery for surgical candidates patients with stage III or IV disease (followed by adjuvant pembrolizumab)* **3.** *For metastatic disease –* • *Immune checkpoint inhibitors –* **a.** *Monoclonal antibodies against cytotoxic T-lymphocyte–associated protein 4 (ipilimumab)* **b.** *PD-1 (nivolumab – pembrolizumab)* • *Targeted therapy against BRAF/NRAS/MEK variants as BRAF/MEK inhibitor combinations (dabrafenib/trametinib)* • *Anti-LAG3 monoclonal antibody (inhibit T-cell proliferation) relatlimab + nivolumab (PD-1)*	
FOLLOW UP	**1.** *Frequent skin self-examinations* **2.** *Regular dermatologist skin evaluations for life every 6 months* ➡ *No routine blood testing or imaging studies if no signs or symptoms in early stages*	
BASAL CELL CARCINOMA (BCC)		
PATHOLOGY	➡ *Arises from epidermal basal cells with association of ultraviolet (UV) radiation from sun exposure*	
INCIDENCE	➡ *The most common skin cancer (esp. in Caucasians) with ↑ incidence due to improved surveillance*	
TYPES	• *Superficial* • *Nodular* • *Complex BCC (cancer in anatomically difficult locations as medial canthus of the eye)*	
HIGH RISK FEATURES OF RECURRENCE	**LOCATION**	➡ *Any tumor size on –* • *Head* • *Neck* • *Hands* • *Feet* • *Pretibia* • *Anogenital*
	SIZE	➡ *≥20 mm in diameter on trunk & extremities (excluding hands & feet)*
	BORDERS	➡ *Poorly defined*
	PATHOLOGY	➡ *Aggressive features (micronodular – sclerosing or mixed infiltrative)*
	HISTORY	**1.** *Lesions of prior radiotherapy sites* **2.** *Recurrent lesions*
	INVASION	➡ *Perineural invasion*
	IMMUNITY	➡ *Immunocompromised patients (transplant/HIV/immunosuppressive therapy)*
PRESENTATION	**MAINLY**	➡ *Localized disease (rare to metastasize with <0.1%)*
	DESCRIPTION	➡ *Translucent pearly papules + Frequent arborizing vessels + Raised borders* **BCC** *Source: John Hendrix* 
	LOCATION	➡ *Typically on sun-exposed areas (but it can occur elsewhere)*
	IF LARGE	➡ *As it spreads by local extension → rodent-eaten appearance (when large)*
DIAGNOSIS	➡ *Shave or punch biopsy*	

TREATMENT	• *Avoid sun exposure* • *Surgical resection/Mohs surgery* • *Electrodesiccation/curettage* • *Cryosurgery* • *Topical chemotherapy* • *Radiation therapy* • *Targeted therapy (vismodegib or sonidegib) for non-surgically candidate complex BCC to reduce the tumor size to allow definitive surgical or radiation therapy*	
FOLLOW-UP	➡ *Consistent dermatologic monitoring*	
NEVOID BASAL CELL CARCINOMA SYNDROME (NBCCS) (GORLIN SYNDROME)		
PATHOLOGY	➡ *Autosomal dominant (AD) with mutation of PTCH1 tumor suppressor gene*	
PRESENTATION	**SKIN**	• *Multiple BCCs* • *Palmar & plantar pits (A) (Source: Amir Mufaddel)*
	SKELETAL	• *Bifid ribs (B) (Source: Hellerhoff)* • *Calcification of the falx cerebri (C) (Source: Amir Mufaddel)* • *Keratocystic odontogenic tumor (mandible bone cyst) (D) (Source: Coronation Dental)*
	EYES	• *Ocular hypertelorism*
		
COMPLICATION	➡ *Medulloblastoma in children (rare)*	
TREATMENT	1. *Regular dermatologist surveillance* 2. *Treatment of BCCs* 3. *Surgical excision of bone cysts*	
PROGNOSIS	➡ *Generally good*	
SQUAMOUS CELL CARCINOMA (SCC)		
PATHOLOGY	➡ *Arise from epidermal keratinocyte cells due to cumulative sun exposure (especially in fair-skinned) in mostly –* • *Face* • *Ears* • *Neck* • *Lips* • *Hands* **SCC** *Source: Dermanonymous*	
RISK FACTORS	**EXPOSURE**	• *Ultraviolet radiation (sun exposure)/Ionizing radiation* • *Radon gas*
	INHERITANCE	• *Family history of SCC* • *Inherited disorders (albinism/xeroderma pigmentosum)*
	IMMUNITY	• *Immunocompromised (organ transplants – chronic lymphocytic leukemia)*
	PRECANCER	• *Actinic keratoses (precancerous skin disorder)*
METASTATIC RISK FACTORS	1. *Size >2 cm* 2. *Depth >4 mm* 3. *Poorly differentiated lesions* 4. *Invasion into nerves & angiolymphatics* 5. *Immunocompromised hosts*	
DIAGNOSIS	➡ *Shave/punch/excisional biopsy with histopathology to confirms the diagnosis*	

<table>
<tr><td rowspan="4">TREATMENT</td><td rowspan="3">SCC</td><td>1ST LINE</td><td colspan="2">➡ Surgical removal with wide 4–6 mm margin via local excision or Mohs surgery for high risk lesions (based on location & size)</td></tr>
<tr><td>IF NON-SURGICAL</td><td colspan="2">➡ Radiation or local cryotherapy</td></tr>
<tr><td>IF METASTATIC</td><td colspan="2">➡ Immunotherapy</td></tr>
<tr><td>SCC IN SITU</td><td colspan="3">• Curettage & electrodesiccation (C&E) • Cryotherapy
• Topical 5-fluorouracil • Topical imiquimod
• Photodynamic therapy • Surgical excision</td></tr>
<tr><td>FOLLOW-UP</td><td colspan="4">➡ Long-term dermatologic follow-up is indicated due to the risk of recurrence & development of other skin cancers</td></tr>
<tr><td colspan="5">SCC IN SITU (BOWEN DISEASE)</td></tr>
<tr><td>PATHOLOGY</td><td colspan="4">➡ Noninvasive form of SCC that is confined to the epidermis & does not spread deeper into the skin (=in situ)</td></tr>
<tr><td>CAUSES</td><td colspan="4">• Sun exposure • Arsenic exposure • HPV genital infection</td></tr>
<tr><td>PRESENTATION</td><td colspan="4">➡ Asymptomatic small red scaly patches that grow slowly over many years
SCC in Situ
Source: Samuel Freire
  </td></tr>
<tr><td colspan="5">MYCOSIS FUNGOIDES & SÉZARY SYNDROME</td></tr>
<tr><td colspan="5">Discussed under T-cell lymphoma</td></tr>
<tr><td colspan="5">PAGET DISEASE OF THE NIPPLE</td></tr>
<tr><td colspan="5">Discussed under Breast Cancer</td></tr>
<tr><td colspan="5">PEUTZ-JEGHERS SYNDROME</td></tr>
<tr><td colspan="5">Discussed under Hamartomas Polyposis Syndromes</td></tr>
<tr><td colspan="5">CUTANEOUS METASTASES</td></tr>
<tr><td colspan="5">➡ 5 Common Cancers –
• Melanoma • Breast cancer • Lung cancer • Colon cancer • Renal cancer</td></tr>
</table>

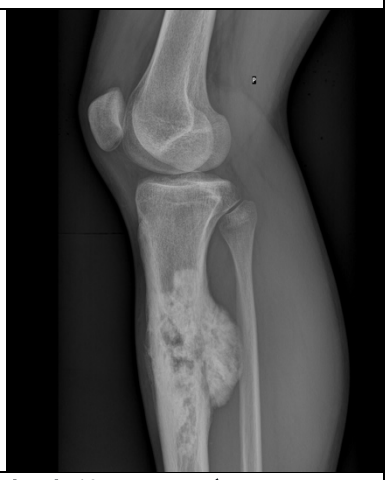
BONE & SOFT TISSUE TUMORS

SARCOMA

OSTEOSARCOMA (OS)

THE MOST COMMON PRIMARY BONE MALIGNANCY

PATHOLOGY		• *Bone sarcoma is aggressive cancer that can arise from multiple locations* • *Ewing sarcoma is very aggressive but less common than osteosarcoma & is mainly pediatric tumor but can be seen in adult patients (the same presentation/diagnostic work-up as osteosarcoma)*
PRESENTATION	**AGE**	➡ *Mostly in children or younger adults but can be found in older adults*
	MAINLY	➡ *Pain at the affected bone site +/- palpable mass*
	10-20%	➡ *Metastatic % with the most common site is the lungs*
DIAGNOSIS	**IMAGING**	• *Assessing the primary location –* 1. *Plain X-ray that shows –* • *Sclerotic changes without clear margins* • *New periosteal formation along the margin of the tumor that causse classic Codman triangle* 2. *CT scan* 3. *MRI* **Tibia Osteosarcoma** *Source: Yousef Samir*
	BIOPSY	• *Core-needle biopsy is preferred (incisional biopsy used only if necessary)* • *Careful with the biopsy tract as it can seed with the cancer cells so it must be part of the surgical resection*
	STAGING	• *Additional imaging needed to assess for metastatic disease*
TREATMENT	**MAINLY**	➡ *Surgery & combination chemotherapy*
	LUNG-ONLY	➡ *Possible cure with surgical resection if lung-only metastatic disease*
	METASTATIC	➡ *Combination chemotherapy for distant metastatic disease*
	EWING	➡ *Local treatment with surgery Or radiotherapy Or both + aggressive combination chemotherapy*



CHONDROSARCOMA

PATHOLOGY	➡ *Consists of formation of cartilage matrix*
TREATMENT	➡ *Surgical resection with no response to systemic chemotherapy & relatively resistant to radiation*

SOFT TISSUE SARCOMA

PRESENTATION		• *Local pain & palpable soft tissue mass*
DIAGNOSIS	**IMAGING**	➡ *CT or MRI to assess the primary tumor site*
	BIOPSY	➡ *Core-need biopsy for confirmation (incisional biopsy used only if necessary)*
STAGING		➡ *Based on –* 1. *Size of tumor* 2. *Grade of tumor* 3. *Depth of tumor*
TREATMENT	**MAIN THERAPY**	➡ *Surgical resection + Neoadjuvant or adjuvant radiation therapy in high-grade tumors*
	METASTATIC	➡ *Systemic chemotherapy*

URGENT/EMERGENT ONCOLOGIC COMPLICATIONS

SUPERIOR VENA CAVA (SVC) SYNDROME

PATHOLOGY

➡ *Obstruction of the superior vena cava (SVC) with the severity of presentation based on –*
1. *The degree of SVC narrowing*
2. *The speed of the SVC syndrome (the slower effect → will allow venous collaterals to develop)*

CAUSES

MALIGNANCY (80%)

➡ *Large mediastinal masses due –*

75%	• *Lung cancer (especially SCLC)*
10%	• *Lymphoma* • *Solid tumors*
5%	• *Germ cell tumors* • *Thymoma* • *Mesothelioma*

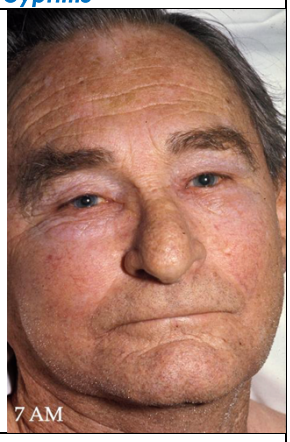
NON-MALIGNANCY

1. *Permanent central venous access (emerging nonmalignant cause)*
2. *Aortic aneurysm*
3. *Goiters*
4. *Fibrosing mediastinitis due to –*
   - *Histoplasmosis* • *Tuberculosis* • *Syphilis*

PRESENTATION

MAINLY

- *Edema of the face/Neck/Arms (usually worse with supine position)*



SVC Syndrome
Source: Herbert Fred & Hendrick Dijk

BLOOD VESSELS

- *Cyanosis/Plethora*
- *Distended cutaneous collateral vessels*

RESPIRATION

- *Cough/Dyspnea (due to tracheal obstruction)*
- *Hoarseness (due to laryngeal edema)*

CNS

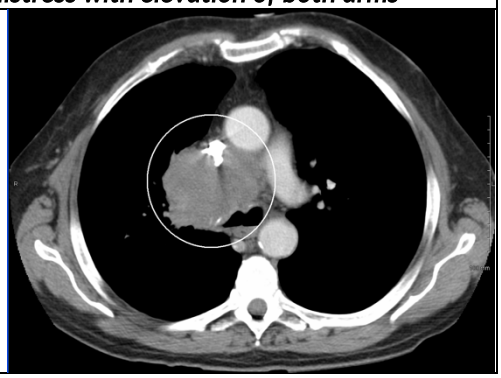
- *Headache (due to ↑ intracranial pressure)*
- *Altered mental status/Syncope (due to cerebral edema)*

EXAMINATION

- *↑ Jugular venous pressure*
- *Stridor (due to airway compression)*
- *Pemberton Sign = facial congestion/cyanosis/respiratory distress with elevation of both arms*

DIAGNOSIS

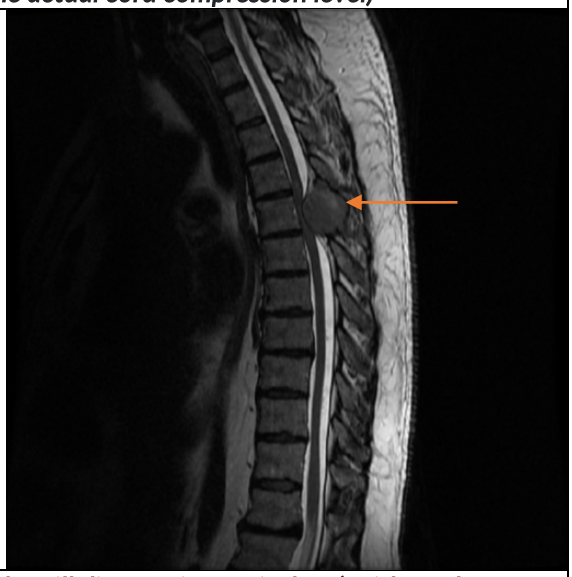
➡ *Confirm the diagnosis with chest CT with IV contrast*



Hilar Mass Causing SVC Syndrome
Source: James Heilman MD

NEOPLASTIC EPIDURAL SPINAL CORD COMPRESSION (ESCC)

INCIDENCE	**2.5%**	➡ *% of ESCC due to metastatic cancer*	
	85%	➡ *% of ESCC due to epidural extension from vertebral body metastases*	
CAUSES	➡ *Most common cancers –* • *Lung cancer* • *Breast cancer* • *Prostate cancer* • *Myeloma* • *Lymphoma with paraspinal mass that extends through the neural foramina → causing ESCC*		
PROGRESSION OF PRESENTATION	**1st**	**VERTEBRAL BODY**	• *Local back pain that worsen overnight (1st symptom that can precede the neurologic manifestation with days/weeks)* • *Increasing narcotic requirement of the patient's bassline pain = concerning of impending cord compression*
	2nd	**NERVE ROOT**	• *Radiculopathy pain that worsen with recumbency*
	3rd	**ANTERIOR COLUMN OF SPINAL CORD**	• *Motor deficit with weakness & long tract signs (spasticity & planter extensor response)*
	4th	**POSTERIOR COLUMN OF SPINAL CORD**	• *Sensory loss*
	5th	**COMPLETE CORD COMPRESSION**	• *Complete paraplegia* • *Sensory loss* • *Autonomic dysfunction –* ○ *Loss of sphincter tone* ○ *Bowel & bladder dysfunction*
EXAMINATION	➡ *Local tenderness (do not delay the work-up in absence of neurologic deficit as early detection of ESCC is crucial to avoid paraplegia)* ➡ *Motor or sensory deficits (usually 1–5 levels below the actual cord compression level)*		
DIAGNOSIS	➡ *MRI with & without contrast of the entire spinal cord (cervical/thoracic/lumbar) is the imaging modality of choice*		



ESCC
Source: Toshkezi G

TREATMENT	**GLUCOCORTICOIDS**	➡ *Immediate therapy (with no delay till diagnostic MRI is done) with moderate- or high-dose glucocorticoids (reduce edema) in suspected ESCC with IV dexamethasone 10 mg loading dose then → 4 - 6 mg every 6 hours*	
	CONSULTATION	➡ *Urgent neurosurgical & radio-oncologic consultations*	
	DEFINITE THERAPY	➡ *Decompression surgery Or Radiation therapy (in radiosensitive tumors as MM/lymphoma/SCLC) Or both (the chances of ambulation is higher with surgery then radiation compared to radiation therapy alone)*	
	OUTCOME	➡ *The most important predictor of outcome is the neurologic status when treatment starts –*	
		80%	• *% of patients that remain ambulatory (giving the face that they were ambulatory when treatment starts*
		20%	• *% of non-ambulatory patients that regain the ability to walk with the treatment*

MALIGNANT EFFUSIONS

MALIGNANT PLEURAL EFFUSIONS

CAUSES

➡ *Most common cancers that are causing malignant pleural effusions –*

- *Breast cancer*
- *Lung cancer*
- *Gastrointestinal tract cancer*
- *Ovarian cancer*
- *Mesotheliomas*
- *Lymphomas*

PATHOLOGY

➡ *3 Underlying etiologies –*

1. *Exudative reactions due to metastases*
2. *Chylous effusions due to lymphatic/thoracic duct obstruction (commonly with NHL)*
3. *Primary pleural malignancy (mesothelioma)*

PRESENTATION

➡ *Progressive dyspnea +/- concomitant pleuritic chest pain*

DIAGNOSIS

INITIAL TEST	• *Chest radiography*
NEXT	• *CT chest (provide more anatomical details)*

TREATMENT

1ST THERAPY	➡ *Thoracentesis for symptomatic effusions with cytology & Light's criteria assessment (refer to pulmonary & critical care chapter)* ➡ *Further treatment is based on –* 1. *Reaccumulation rate* 2. *Severity of symptoms* 3. *Patient's prognosis*	
RECURRENT	**SLOW RECURRENCE**	➡ *Repeat therapeutic thoracentesis + Treat underlying cancer*
	RAPID RECURRENCE	➡ *Insertion of indwelling pleural catheter or pleurodesis*

MALIGNANT PERICARDIAL EFFUSION

INCIDENCE

➡ *13-23% of pericardial effusion are malignant (can be the 1st sign of malignant disease)*

CAUSES

➡ *Most common cancers that are causing malignant pericardial effusions due to local disease extension into the pericardium or hematogenous spread –*

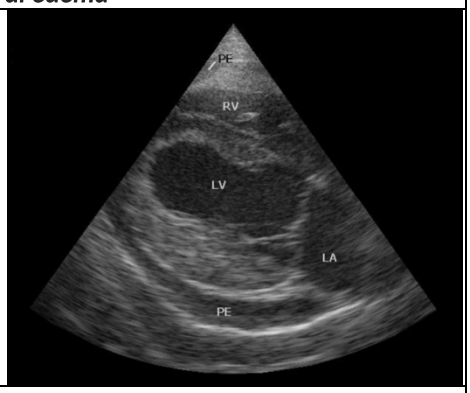
- *Lung cancer*
- *Breast cancer*
- *Esophageal cancers*
- *Melanoma*
- *Lymphoma*
- *Leukemia*

PRESENTATION

- *Dyspnea*
- *Chest discomfort*
- *Fatigue*
- *Cardiac tamponade (causing ↓ cardiac output due to biventricular filling impairment) presentation –*
  - *↑ JV distention*
  - *Hypotension/muffled heart sounds*
  - *Pulsus paradoxus*
  - *Peripheral edema*

DIAGNOSIS

➡ *Echocardiography*



Pericardial Effusion (PE)
Source: Kalmut

TREATMENT

- *For symptomatic pericardial effusion –*

➡ *Percutaneous pericardiocentesis or surgical drainage via pericardial window & cytology assessment*

MALIGNANT ASCITES

CAUSES

➡ *Most common cancers that are causing malignant ascites (due to peritoneal seeding of the malignancy) –*

- *Ovarian cancer (Meigs syndrome/the most common)*
- *All GI cancers*
- *Breast cancers*
- *Urothelial cancers*
- *NHL*

TREATMENT

- *Paracentesis (diagnostic & therapeutic)*
- *Peritoneal catheters for palliative therapy in refractory cases*